

This paper is also published as supplement no. 666 to
Acta Medica Scandinavica

The natural history of rheumatic fever and rheumatic heart disease in Malmö

By Bertil Persson

Rund 1982.





Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41552406_0023

The natural history of rheumatic fever and
rheumatic heart disease in Malmö

by Bertil Persson

From the Department of Medicine, University of Lund,
Malmö General Hospital, Malmö, Sweden

THE NATURAL HISTORY OF RHEUMATIC FEVER AND
RHEUMATIC HEART DISEASE IN MALMÖ

by

Bertil Persson

with a special chapter on roentgen findings
by Bertil Persson and Peter Aspelin

translated by L. James Brown



CONTENTS

Chapter I	Introduction	11
Chapter II	Survey of literature	13
I.	Historical landmarks	13
II.	Rheumatic fever epidemiology	14
A.	Frequencies	14
1.	Environmental and economic factors	16
2.	Density and structure of population	16
3.	Climate	16
4.	Hereditry	17
B.	Course of rheumatic fever	17
1.	Carditis	17
2.	Time course	18
3.	Special symptoms	19
C.	Chorea minor	19
D.	Beta-hemolytic streptococci	20
E.	Immunology	20
1.	Chemistry	20
2.	Antistreptolysin	21
3.	Other serological tests	21
4.	Immunofluorescence	22
5.	Rheumatoid arthritis - factors	23
F.	Therapy in classical rheumatic fever	23
1.	Pharmacotherapy	23
2.	Tonsillectomy and vaccination	24
3.	Prophylaxis	24
G.	Other microorganisms causing heart damage	26
1.	Virus and endocarditis	26
2.	Ornithosis	27
H.	Cause of heart injury	27
III.	Rheumatic heart disease, epidemiology	28
A.	Frequencies	28
B.	Rheumatic heart disease - natural history	30
1.	Course	30
2.	Time course	32
C.	Pathology of the valves	33
1.	Rheumatoid arthritis and valvular defects	34
D.	Clinical evaluation	35
1.	Roentgenology	35
2.	Digitalis levels	35
E.	Complications	35
1.	Hemolytic anemia	35
2.	Thromboembolism	36
F.	Therapy	36
1.	Anticoagulation	36
2.	Defibrillation	37
3.	Operation	37
4.	Operation in the active rheumatic phase	39
G.	Valvular disease and pregnancy	39

Chapter III	Material and methods	40
I.	The town of Malmö	40
II.	The material	42
III.	The review	43
	A. Review in 1961	44
	B. Review in 1974	44
	C. Autopsies	47
	D. Representativity of Hall's material	47
	E. Statistics	48
	F. Virology	48
IV.	Reference material	48
V.	Composition of rheumatic fever series reviewed	49
Chapter IV	Classification	50
I.	Acute rheumatic fever	50
	A. Criteria	50
	B. Criteria for rheumatic fever in our study	50
	1. Major criteria	51
	2. Minor criteria	52
	3. Comments	53
II.	Rheumatic heart disease	54
	A. Criteria	54
	1. Comments	55
Chapter V	Rheumatic fever	56
I.	Frequency	56
	A. Variation of frequency of rheumatic fever with the population of Malmö during the study periods	56
	B. Frequency of criterial symptoms and signs	56
	C. Age at onset	58
	D. Age at onset of rheumatic fever and recurrences	58
	E. Sex distribution	58
	F. Distribution of primary attacks and recurrences during the study periods	58
	G. Distribution in the period of the two materials	60
II.	Special groups of interest	62
	A. Patients with only carditis, polyarthrititis or chorea without co-existing rheumatic fever	62
	B. Nephritis in rheumatic fever	62
	C. Scarlatina	62
	D. Diphtheria	64
	E. Diphtheria and scarlatina in Sweden from 1918	64
	F. Erythema nodosum	64
	G. Ornithosis and rheumatic fever	66
III.	Relation between rheumatic fever, carditis and chorea	66
	A. Age at onset	66
	B. Chorea	68
	C. Carditis	68
	D. Cases of isolated chorea or carditis	68
IV.	History and physical findings	68
	A. Anamnestic data in rheumatic fever	68
	B. Height, weight and blood pressure	70
V.	Immunological tests	70
	A. Antistreptolysin titre	70
	B. Rheumatoid factor	71
VI.	Rheumatoid arthritis and Bechterew's disease in rheumatic fever and rheumatic valvular disease	71
VII.	Rheumatic fever - socio-economic considerations	72

A. Geographical considerations	72
1. Socio-economic distribution in Malmö in relation to the frequency of rheumatic fever	72
2. Rheumatic fever	72
B. Family income and rheumatic fever	77
C. Distribution of rheumatic fever among social groups	77
Chapter VI Rheumatic fever and rheumatic lesions	81
I. Development of lesions per 5-year period after diagnosis of rheumatic fever	81
II. Rheumatic fever in the series with VOC	84
A. Distribution of material among different types of VOC	84
B. Relation between year of rheumatic fever and type of VOC	84
C. Frequency of rheumatic fever found at review of patients with VOC	84
III. Age at onset of VOC in patients with and without rheumatic fever	84
IV. Age at onset of rheumatic fever	86
A. Survey of degree of probability of rheumatic fever	88
V. Penicillin therapy	88
A. Distribution of penicillin treatment according to year of rheumatic fever	88
VI. Cortisone therapy in rheumatic fever and its effect on development of heart lesions	89
Chapter VII Rheumatic lesions	90
I. Patients still alive and reviewed	90
II. Types of lesions in relation to rheumatic fever	90
III. Frequencies	90
A. Rheumatic lesions with and without previous rheumatic fever	92
B. Variation of frequency of rheumatic lesions	92
C. Time distribution	92
D. Age at diagnosis of lesions	94
E. Sex distribution	94
IV. Earlier natural history and symptoms of defects of the mitral and of the aortic valves	94
V. Medical history before diagnosis	96
VI. Findings at review	96
A. Physical findings	96
B. Hypertension	97
C. ESR	97
D. Haptoglobin	97
E. Diuretics and potassium in the entire material of rheumatic fever and rheumatic lesions	99
F. Plasma digoxin level in the entire material	99
G. Immunological findings	99
VII. ECG changes in patients with lesions	101
A. Pacemakers	102
VIII. Spirometric findings in patients with rheumatic lesions	102
IX. Medical history after diagnosis	104
X. Complications	106
A. Interval between onset of symptoms and diagnosis	106
B. Working capacity	106
XI. Fertility	108

Chapter VIII	Radiological findings in patients with cardiac lesions	110
	Authors: Bertil Persson and Peter Aspelin	
I.	Radiological findings	110
A.	Mitral lesions	110
B.	Aortic lesions	112
C.	Bivalvular and other lesions	112
D.	Heart volume	112
E.	Comparison between clinical and radiological diagnoses	112
II.	Cineradiography of the heart	114
A.	Calcifications in the heart	114
Chapter IX	Rheumatic heart disease - natural history	116
I.	Age factors	116
A.	Age at diagnosis of cardiac lesions	116
B.	Frequency of complications and therapy	116
1.	Material of VOC in 1955-70	118
C.	Therapy	118
1.	Comparison between treated and untreated patients	120
D.	Frequency of heart surgery	120
1.	Prostheses	122
E.	Vascular lesions	122
II.	Natural history of different types of lesions	122
A.	Mitral lesions	122
1.	Time course	122
2.	Defibrillation and operation	124
3.	Course of mitral lesions from the time of diagnosis to death	124
B.	Aortic lesions	124
1.	Time course	124
2.	Defibrillation and operation	127
3.	Course of aortic lesions from the time of diagnosis to death	127
C.	Double lesions	127
1.	Time course	127
2.	Defibrillation and operation	127
3.	Course of double valvular lesions from the time of diagnosis to death	129
III.	Interval between diagnosis and symptoms during the study period	129
A.	Rheumatic fever series	129
B.	Rheumatic lesions	131
Chapter X	Autopsied patients	134
I.	Rheumatic fever	134
A.	Year of death and its relation to rheumatic fever	134
B.	Primary cause of death	134
1.	The present material	136
2.	Hall's material	136
II.	Lesions	137
A.	Time factors	137
B.	Year of death	140
C.	Primary cause of death	140
D.	Secondary cause of death	140

General Summary	143
A. Short historic survey	143
B. Material and methods in this study	143
C. Rheumatic fever	144
D. Rheumatic valvular lesion	145
E. Patients who had died	149
F. Concluding remarks	150
Acknowledgements	151
References	152

CHAPTER I

INTRODUCTION

Rheumatic fever is a disease caused by cross-reacting antibodies to beta-hemolytic streptococci, reacting with human tissues. In a group of the patients this leads to chronic cardiac valvular lesions. The frequency of rheumatic fever is decreasing in the whole world. The decline is steepest in the industrialized countries, where the disease is now relatively uncommon. Many authors ascribe this to better socio-economic and hygienic or housing conditions and improved nutrition. We have therefore studied this trend in a highly industrialized, economically well-to-do country like Sweden.

The purposes of the present study are:

- to elucidate the natural history of rheumatic fever,
- to shed light on the natural history of rheumatic heart disease,
- to study the changes in the clinical picture of acute rheumatic fever with time and their possible causes,
- to find out to what extent such changes affect the clinical picture of organic heart defects,
- to form an opinion of the cardiac status in a selected population, and
- to try to evaluate the effect of penicillin treatment in rheumatic fever on the development of rheumatic heart disease.

Rheumatic fever and its natural course during the years 1930-1970 and the rheumatic lesions during 1955-1970 were analysed. They were compared with the findings made by Hall in his study of heart disease in 1930-1954.

Rheumatic fever declined markedly through the entire period, except for a short increase in frequency in association with the second World War, when the socio-economic standard of the country was lower. Findings in our material argued strongly for poor socio-economic status playing a role in the problem of rheumatic fever. Whether penicillin therapy and prophylaxis also contributed to the decrease in frequency could not be decided with certainty. Separate analyses of patients who had or had not been treated with penicillin produced no convincing evidence of penicillin being responsible for the decline in the frequency of rheumatic fever. As expected from studies in other countries, rheumatic fever had occurred

somewhat more often in females than in males.

It is remarkable that observed diagnosed lesions of the type called rheumatic did not show the same marked decrease during the study period. It should, however, be mentioned that the number of lesions in patients who had earlier in life had rheumatic fever has continuously decreased. The relation mitral lesions with an early onset to aortic lesions with a relatively late onset was changed. No decisive change in the actual course of the heart disease during the study period was found.

As for the results of treatment, the surviving patients appeared to have been adequately treated and to be in a relatively good general condition, but the social consequences in the form of loss of working capacity due to heart lesions were considerable. Strangely enough, underdigitalization was by no means uncommon; neither was hypopotassemia in patients receiving diuretics.

Spirometry showed moderately decreased pulmonary ventilation, but otherwise nothing remarkable. Good agreement was found between the clinical and roentgenological findings, and usually the roentgenographic changes found were in accord with the clinical pictures.

In the patients who had died, the frequency of earlier rheumatic fever was lower and the duration of survival after the diagnosis was shorter, probably because the lesions had been detected so late in their course. Most deaths could be ascribed directly to the lesions and subsequent incompensation.

In summary, then, rheumatic fever has been rapidly decreasing in frequency throughout the entire study period, while that of the heart lesions had persisted largely unchanged, though the proportion of early mitral lesions was becoming smaller and that of late aortic lesions, larger.

Chapter II

SURVEY OF LITERATURE

I. Historical landmarks

Although de Baillou (23) gave his classical description of acute polyarthrititis already in the seventeenth century, the many names given to this disease show that it is not a well-defined clinical entity.

Names such as rheuma, rheumatism, Bouillaud's disease (46), polyarthrititis subacuta, rheumatismus, polyarthrititis acuta, polyarthrititis rheumatica acuta, rheumatismus infectiosus, rheumatismus verus, morbus rheumaticus specificus have been used to designate the disease now called acute rheumatic fever. In 1778 Pitcairn (251) showed that cardiac disease was more common in patients with acute rheumatic fever than in the population in general, and in 1840 Bouillaud (46) presented the Law of Coincidence, according to which acute rheumatic fever is associated with heart changes, and that this coincidence is the rule rather than the exception. In 1835 Watson (353) reported that the disease was most common in childhood, and that the risk of cardiac complications decreased with increasing age of the patient. Sydenham (314) described chorea minor during the seventeenth century, but Begbie (26) was one of the first to observe the correlation between this disease and acute polyarthrititis and endocarditis. The intimate correlation between these two diseases was, however, established by the work of Roger (261) in the middle of the nineteenth century. Although rheumatic nodules were described in 1812 by Wells (356) it was not until 1881 that Barlow and Warner (24) pointed out the correlation between nodules, chorea and acute rheumatic fever. Erythema marginatum was first described in 1831 by Bright (47), who had observed roseola annulata in chorea minor. In 1940 Hedley (145) claimed that the first monograph on rheumatic fever was published in 1888 by Haygarth (144), who is said to have been the first to use the term acute rheumatic fever. In 1907 Schick (271) reported the late manifestations on an allergic basis after scarlatina.

II. Rheumatic fever, epidemiology

A. Frequencies

Numerous epidemiological reports have been published since the beginning of the century. Hall (136) surveyed the literature up to the end of the 1950s. Since then several authors have described a change in the picture of rheumatic fever and, above all, a markedly decreasing incidence.

The 3 % frequency of attacks of rheumatic fever often reported in association with epidemics among military populations has been questioned by Stollerman (302), who also stressed that no particular type or strain of group A streptococci had been found that could be regarded as rheumatogenic. Somer (288) underlined that rheumatic fever had now become a relatively uncommon and clinically mild condition probably leading less frequently to chronic heart disease, but that asymptomatic and therefore untreated carditis can impair the expected favourable prognosis. The lower virulence due to the decreasing frequency of epidemic strains is thought to explain the decreasing frequency and severity of rheumatic fever.

Hall's (136) thesis on rheumatic fever in Malmö in 1930-44 is often quoted in the literature and will be frequently referred to in subsequent chapters. Sievers and Hall (285) found the incidence of acute rheumatic fever in Malmö to have fallen from 0.40 per 10 000 inhabitants in 1955-59 to 0.13 in 1960-64. Ekelund et al. (95) found in 4 Swedish materials that the incidence in 1952-56 was 0.90 per 10 000 children, but only 0.23 in 1957-61.

In 1966 Tybjaerg-Hansen (335) reported an incidence of 0.15 per 10 000 inhabitants in Copenhagen. Crawford (76) reported that there were only 4 cases of rheumatic fever in 1970-72 in Nottingham in England.

As for countries outside Scandinavia, Witczyńska (370) in Poland found a decrease from 1.14 o/oo in 1965 to 0.45 in 1971. Sashenkova and Chebotareva (269) and Nesterov (232) reported a decline in the incidence and severity of the course of the disease. From 1961 to 1968 Sitaj et al. (286) in Czechoslovakia found a decrease from 53 to 15 per 100 000 inhabitants. According to an editorial (89) in the Lancet, the frequency in Birmingham fell from 116 to 44 per 100 000 inhabitants from 1938 to 1944 and from 116 to 29 from 1945 to 1955 in San Francisco.

Besterman (30) found the prevalence in Denver in 1967 to be 1.7 per 1 000 inhabitants. He also reported a prevalence of 0.6 in Toronto and of 1.8 in Osaka, while the frequency per 1 000 inhabitants in 1937 was as high as 7.7 in London, 7 in Israel (Tel-Aviv) and 16 in Jordan. Decreases have also been reported by Mayer et al. (213), Acheson (2), Brownell (50) and Noonan (233).

Markowitz and Kuttner (208) gave an incidence of 100-120 per 100 000 children, aged 5-15, in Chicago in 1928-42, compared with a frequency of only 50

in 1962. Quinn and Federspiel (253) reported an incidence of 14.9 cases per 100 000 inhabitants that fell to 6.4 from 1963 to 1969.

However, Stollerman and Pearce (304) reported that in Memphis in 1968 all the patients with polyarthrititis seen at the emergency department were admitted to hospital and that the frequency of rheumatic fever among them was surprisingly high, but he gave no figures.

Hong (156) reported the frequency of rheumatic fever among all hospitalized patients in Korea to be between 0.2 and 0.9 % and Shiokawa (277, 279) and Shiokawa and Murakami (281) found a strong decline in the number of patients with rheumatic fever in Japan and a reduction in the number of fatal cases of the condition to 0.06 per million. According to Glover (125), the number of deaths from rheumatic fever per million inhabitants in England fell from 60 to 12 between 1913 and 1943. He (124) also described a reduction to one third in USA from 1900 to 1932. But the frequency reached a peak in the American army during the second world war.

Massell et al. in Boston (211) claimed that a cyclic variation in the incidence of streptococcal infection of the joints leads to a cyclic variation of rheumatic fever. According to Strasser (305), an occurrence of 200 000 cases of throat infection implies 40 000 cases of streptococcal infection, 600 cases of rheumatic fever and 100 cases of rheumatic cardiopathy. Ferencz of Buffalo (111) was of the opinion that less than 1 % of all streptococcal infections are followed by rheumatic fever.

The situation in Asia was somewhat different. According to Bhattacharya et al. (31) in Varanasi in India, Homma (154) in Keio and Gharib (122) in Iran, carditis is the most common manifestation of acute rheumatic fever. In northern India Sanyal et al. (268), however, found a clinical profile corresponding to that in the western countries. Arthritis was found in 66 %, chorea in 20.7 % and carditis in 33.7 %. Engleman et al. (97) reported a brighter prognosis of heart disease in rheumatic fever in adult age. Massell (210) and Taranta (320) found acute or chronic heart disease to increase the risk of rheumatic fever. Wilson et al. (363) found the frequency of recurrence to be higher soon after the first attack of rheumatic fever and in the lower socio-economic groups. Spagnuolo et al. (292) found the risk of a recurrence to increase with the number of preceding recurrences, and Perry (247) found the frequency of heart complications to increase with the number of recurrences. Chen et al. (64) followed up 316 school-children in Malaysia, where the accumulated percentage of children with a positive throat swab with or without other signs of infection was 100 for all streptococci and 93 for group A streptococci during a one-year study.

1. Environmental and economic factors

Strasser (306) found that rheumatic fever was more common in subtropical and tropical countries than in the temperate, industrialized western countries, and that poor social conditions were a more important etiological factor than climatic conditions, but that the frequency of the disease was continuously declining in poverty stricken enclaves.

In 1930 Glover (124) reported that rheumatic fever can be 30 times more common among children in poor areas than among those in well-to-do families in industrial towns.

According to an editorial in the Lancet (89), children of unskilled labourers had rheumatic fever much more often than children of skilled workers, and latitude, altitude, density of population and economic factors as well as age play an important role. Cumming (80) also found that poverty and density of population increase the incidence. In USA Pilapil and Watson (250), Besterman (30) and Brownell and Bailen-Rose (50) found the incidence in the living areas of the lowest income classes to be 2-3 times higher than that in the dwelling areas of the middle and high-income classes. Kudryavtseva and Polunin (183) pointed out that the course of rheumatic fever is less favourable in association with a high general morbidity among the children, living in poor homes and together with unhealthy parents.

2. Density and structure of population

Acheson (2) showed that in USA the risk is higher in towns and in large families, i.e. it increases with the population density. According to Ferencz (111) in Buffalo, patients with rheumatic fever are poor and not properly nourished, but often live in astonishingly large houses. Gordis et al. (129) claimed that in every socio-economic class the incidence was higher among non-whites than among whites. In the whites the incidence of rheumatic fever decreased with increasing socio-economic standard, but not among the non-whites. Markowitz and Kuttner (208) stated that rheumatic fever was least common in southern USA and California and that from the 1920s, it had become more common among the coloured, in whom it had formerly been less common. Tamer (319) found the frequency in South Florida, to be high among the 5-15-year-old coloured living in densely populated areas in the town centres. Several reports (299) give higher frequencies for such collections of people as camps.

3. Climate

Wedum and Wedum (354) and Acheson (2) gave a high frequency of rheumatic fever for dry areas and high altitudes, especially in association with inability to

control the microclimate. Morton (224), on the other hand, found no such evidence for altitudes between 3 500 and 10 150 feet. In a study of the islands off the coast of Estonia, Kyrge et al. (187) found no correlation between rheumatic fever, on one hand, and atmospheric temperature, number of hours of sunshine, total radiation and relative humidity of a maritime climate on the other. Taranta (321) gave a lower frequency for equatorial than for temperate regions. Sashenkova and Chebotareva (269) described seasonal changes in the frequency. Tahernia et al. (316) in South Iran found a high frequency in November and December and Saksena et al. (266) reported an increased frequency in November and January.

4. Heredity

Borsche (45) reported endogenous predisposing factors in the form of age and hereditary factors. Olney (241) and Gray et al. (132) felt that susceptibility to rheumatic fever may be hereditary due to a single autosomal recessive gene. Uchida (336) stated that if we assume a markedly reduced penetrance, both a single recessive and single dominant heredity would seem possible. According to Christian (69), the incidence of blood group 0 is lower among patients with rheumatic fever than among controls. Marcus (204) contended that the debate on the significance of the ABO system for rheumatic fever had not resulted in any definite conclusions. Stevenson and Cheeseman (298), who studied 462 families, concluded that hereditary factors play an important role, while Coste et al. (74) were less convinced. Griffith et al. (133) showed that patients who had had an initial attack of rheumatic fever at home did not have recurrences after they had moved away from their families. Reports on tissue types are few, but Falk et al. (101) studied HL-A antigen in patients with rheumatic fever. They found that the incidence of A-3 tended to be lower and that the frequency of common antigens was higher among the parents.

B. Course of rheumatic fever

Comprehensive surveys have been published by Markowitz and Gordis (207), Hollander and McCarty (153) and in a monograph entitled Rheumatic Fever (90).

1. Carditis

According to Edström (91), rheumatic fever can be monocyclic, polycyclic or progressive with involvement of the heart, vessels, lungs, pleurae, kidneys, central nervous system, eyes, skin and subcutaneous tissue. Clinical findings differ from morphological changes and, for example, the pericardium is involved in 10 % and 49 % according to respective clinical and pathological findings.

Bock (41) underlined that in rheumatic fever not all murmurs are of organic origin, but at the same time pointed out that in 60 of 89 cases with rheumatic carditis the disease led to permanent valvular lesions. Wilkoszewski (360) reported that episodes during the 1960s were more benign than in the 1950s and that the reaction of the heart was less intensive. Ward and Deasy (351) found the course in boys to be less severe than in girls, but that practically all with permanent valvular lesions had had carditis. In 1951 Bland and Duckett Jones (39) found in a follow-up of at least 20 years that of more than 1 000 patients, 44 % had signs of valvular disease. Rheumatic fever recurred in one out of every five cases within the first 5 years, in one out of 10 during the next five years, and in one out of 20 in the subsequent 5 years. Feinstein et al. (110) followed up 441 children for 8 years. Those who had no signs of murmurs initially were free from rheumatic heart disease. The late prognosis depended to a large extent on the initial size of the heart. Feinstein and Di Massa (103) found no correlation between prolongation of the PR-interval and later cardiac lesions, while enlargement of the heart, heart failure and pericardial rubbing in rheumatic fever occur almost exclusively in patients who later develop valvular disease. In a series of patients with valvulitis initially, 67 % had rheumatic heart disease within 5 years compared with 0 % of those without valvulitis. Barnert et al. (25) reported carditis in 15 % in acute rheumatic fever. Kuttner and Mayer (186) showed that three fourths of the patients followed up showed a similar pattern in second attacks of rheumatic fever. Findlay and Fowler (113) found no noteworthy difference in frequency of carditis after rheumatic fever in 1937-40 and that in 1957-60.

2. Time course

Feinstein (102) and Feinstein et al. (107) claimed that the interval between streptococcal infection and rheumatic fever, previously thought to be 2 weeks, may be both longer or shorter. Rheumatic fever does not occur without an increase in the antibodies against streptococci, while patients with such an increase can develop rheumatic fever without preceding soreness of the throat or a positive culture. Feinstein and Spagnuolo (104) found that the acute inflammatory activity lasted 109^{+57} days in a series in which the corresponding value for those with valvular involvement was 124 days, and for the others, 89 days. Taranta et al. (325) reported 76 cases in which the activity lasted more than 223 days, which was formerly regarded as above the upper normal limit. Reuschel et al. (358) and Besterman (30) stated that the subacute course in adults had increased in frequency and Gavrin et al. (120) stressed the practical difficulties encountered in a careful follow-up of such series.

3. Special symptoms

Burda and Sanders (55) discuss the concept that rheumatic fever may cause a deforming arthritis which superficially simulates rheumatoid arthritis. This chronic postrheumatic fever (Jaccoud's) arthritis is defined by Bywater's and Zvaifler's criteria and has been reported in 15 cases since 1869. It differs from rheumatoid arthritis by the presence of migratory polyarthritis and rheumatic valvular engagement. Carvalhal et al. (62) described 32 cases of rheumatoid pulmonary disease and Shulman et al. (283) stated that abdominal pain is not an infrequent symptom of acute rheumatic fever and may occur alone or in association with major manifestations of that disease. In some materials $2\frac{1}{2}$ % underwent appendectomy prior to the establishment of the correct diagnosis.

C. Chorea minor

Judging from most materials on record, the frequency of chorea is markedly decreasing. Lewis-Johnsson (196) gave 9 years as the age at onset in boys as well as in girls with equal frequency in both, while Lessof (194) thought that chorea was twice as common in girls as in boys, and that after 15 years of age the girl/boy ratio of severe attacks was as high as 18:1. The movements of chorea lasted from one week to one year, and the incidence of carditis in association with the first attack was 73 %. Taranta and Stollerman (326) found the titer of antibodies to streptococci to be high in the early stage of chorea and the lag period between streptococcal infection and chorea minor to be longer than in rheumatic fever. Immunological studies of the cerebrospinal fluid revealed nothing about the pathogenesis of the condition.

Wendler (357) postulated that chorea minor and rheumatic fever are two distinctly different diseases with a common etiological factor and that hereditary factors decide which of the two conditions will develop. These factors often, though not always, occur together. He felt that isolated chorea cannot be regarded as rheumatic if the ESR is normal. Aron et al. (16) reported that 27 % of their patients with isolated chorea developed rheumatic valvular disease.

Neither did the last-mentioned authors find any neurological sequelae after chorea, though psychoneurotic problems were common, a finding also made by Stehbens and Macqueen (297) and Schmidt (272). EEG studies of rheumatic fever and chorea minor by Schmidt (272) revealed rheumatic encephalopathy in 81 % of the patients examined. Of these patients, 11 % developed chorea minor and 3 % were found to have somnolent convulsive or parietic encephalopathy. The EEG changes in chorea and in rheumatic fever without chorea were similar. Of 211 patients reviewed after rheumatic fever, 40 % had cerebral sequelae, while only 3 % had any important disease of the CNS. Ertugrul et al. (99) found the frequency of EEG

changes to be 29 % in chorea and 94 % in carditis.

D. Beta-hemolytic streptococci

Schick (271) claimed (1907) in his classical article that streptococci are the cause of rheumatic fever, and Lancefield (190) in 1962 published the classical investigation on M antigens in streptococci.

Stollerman (300, 301) pointed out that a group A streptococcal infection not producing an immune response does not cause primary or secondary rheumatic fever.

The frequency of rheumatic fever in streptococcal infection varies with the presence or absence of rheumatic heart disease, with the interval since the last of rheumatic attacks as well as with the virulence of the streptococcal strain, which in turn depends on the epidemiological situation in the population. Dunlap and Bergin (86) reported that the incidence of sequelae among earlier carriers of streptococci was 0.2 % after the first attack of rheumatic fever, 0.2 % after a recurrence, and 0.2 % after glomerulonephritis or a total of 0.6 %. Late sequelae after rheumatic fever were almost always due to new types of streptococci that had not previously occurred in the patient.

According to Stollerman (300), the risk of recurrences even after 5 years of prophylaxis is great if the rheumatic patient contracts an infection with virulent streptococci. Ayoub (18) reported a recurrence frequency of 50 % in patients with rheumatic fever. Stollerman (302) also underlined that some strains of streptococci seem to be capable of producing rheumatic fever; some nephritis; and some, both or neither. Bisno et al. (33) claimed that pyoderma strains are not often associated with rheumatic fever, but often with glomerulonephritis. Wannamaker (346) also stressed the difference between streptococcal infections of the throat and of the skin. Since only certain serotypes of streptococci occur in pyoderma it is possible that these strains lack some property of importance in the pathogenesis of rheumatic fever. Ayoub among others (18) showed that 80-85 % of the strains in man belong to group A and that the occurrence of these has decreased in the white population and increased in the coloured in USA. Also in his study rheumatic fever rarely followed pyoderma and occurred with a frequency of 3 % in cases of pharyngitis.

Kawakita et al. (173) and Shiokawa of Japan (276, 278) showed in India a varying dominance of the various serotypes in different districts and at different times.

E. Immunology

1. Chemistry

Okuni and Fujikawa (238) claimed that ASP (antistreptococcal polysaccharide),

which is believed to be of specific clinical importance in the diagnosis of rheumatic fever because of the antigen common to human valvular disease and glycoproteins in the cell wall in group A streptococci. In a number of animal experiments Ginsburg (123) has distinctly shown that streptococci can injure cells and tissues. McCarty (214) found cross reactions between streptococcal hyaluronic acid and human hyaluronic acid and protein polysaccharides as well as between group A polysaccharide and glycoproteins in the valves, membrane protein and sarcolemma in the heart and skeletal muscles. He thought that interaction between two or more of these factors is necessary to trigger off the disease.

2. Antistreptolysin

Group A streptococci were classed serologically by Lancefield (190), who also described antistreptolysin O. He distinguished between two surface proteins, M and T antigen. Stollerman and Pearce (304) claimed that immunity against infection with very virulent M-rich strains is stable only in individuals infected earlier with homologous M type. In contrast with antistreptolysin O and other antibodies against extracellular products, antibodies against M protein develop slowly. It is therefore difficult to suppress the AST response completely, while antibodies against M antigen are easily suppressed by chemotherapeutics. Lancefield was of the opinion that patients with rheumatic heart disease are the most sensibilised hosts for rheumatic fever. Tichy (330) showed that ASL is positive in 2.75 %, also in those with a firm diagnosis of rheumatoid arthritis. Vorlaender and Lorbacher (340) thought that in rheumatic carditis the cause of the disease is the deposition of circulating antigen-antibody complexes in certain tissues or vascular areas.

Todd's (332) classical study showed that in patients with rheumatic fever and bacteriologically demonstrated hemolytic streptococci the antistreptolysin titers are just as high as in such patients not examined bacteriologically.

3. Other serological tests

Several tests have been used to diagnose streptococcal infections immunologically. Wannamaker and Kaplan (349) described the antihyaluronidase test (AH), antiNADase and antiDNase, which combined have a diagnostic accuracy of 95 %. They postulated, however, that tests for anti-group A carbohydrate heart reactive antibody, M antibody and M associated protein antibody can be used in research, but not yet clinically. AntiNADase is valuable mainly in acute nephritis because type 12 strains produce much of this enzyme. Kumagai (184) recommended also the use of the antistreptolysin test (AST) but in combination with other antibody tests. Quinn and Liao (254) compared streptococcal agglutinin, antihyaluronidase, antistreptolysin O and antistreptokinase and found no difference in antibody response. Rolicka and

Massell (262) described a test for antipeptidoglycan and claimed that patients with this substance in their serum do not develop carditis. Wannamaker and Ayoub (348), Ayoub and Wannamaker (19), Mihai et al. (221) and Watanabe (352) stressed that no specific test for acute rheumatic fever was available, but that a combination of several tests gives a higher diagnostic accuracy. AST is the test most widely used and is probably the best. Antihyaluronidase and anti-diphosphopyridin-nucleotidase tests are recommended as secondary tests.

Klein and Klein (179) expressed the view that the ASL reaction is the most sensitive test, but at the same time recommended also determination of anti-streptokinase as a secondary method. Ayoub and Wannamaker (20) determined simultaneously AST, antiDNase B and antiNADase in patients with chorea and found all to be significantly increased compared with the results in controls, though 10 of 30 patients showed no increase in AST.

Wood and McCarty (371) postulated that the test gives the clinician valuable information about the persistence of the rheumatic disease. Anderson and McCarty (9) thought that C-reactive protein was the most sensitive test for rheumatic activity and that serum mucoprotein can indicate persisting activity. Burgio and Vaccaro (57) found that IgG, IgA, IgM and β_{1C} -globulin levels were significantly increased in children with rheumatic fever. Cuppari et al. (81) found that lymphocyte transformation with streptolysin preparations was significantly decreased in patients with their first attack of rheumatic fever, but not in those with a recurrence.

4. Immunofluorescence

Zabriskie (379) showed that sera from patients with acute rheumatic fever showed binding of antibodies to heart tissue in fluorescence microscopy.

The fluorescent pattern was compatible with that of antisera against pure streptococcal membranes. The intensity of the fluorescence was much stronger in sera from patients with acute rheumatic fever than from patients with uncomplicated streptococcal infections. Patients who had undergone heart surgery also had higher titers of heart reacting antibodies. The antibodies began to decrease in titer after 1-2 years. In those who had undergone cardiectomy the antibodies were adsorbed only to the heart tissue, but not to the streptococcal membranes. He thought that the divided antigenicity between group A streptococci and human tissue might be due to long adaptation to the host. Hess et al. (150) studied serum factors that reacted with human heart muscle of the patients with rheumatic fever, 41.5 % had a sarcolemma-sarcolemma pattern. The corresponding figure for those patients with carditis was 63.4 %.

Vazquez and Dixon (339) found the heart to contain gammaglobulins in

significant concentrations in active rheumatic carditis. Vaccaro (337) and Burgio and Vaccaro (56) demonstrated that cross-reacting antibodies between streptococci and the heart decreased after the acute phase of rheumatic fever. Cavelti (63) showed auto-antibodies to human heart in 75 % of a groups of patients with rheumatic fever. Kaplan (168) described a number of serological methods for detecting heart-reacting factors. He also showed streptococcal cross-reacting auto-antibodies against the heart in 55 % of patients with rheumatic heart disease as well as in 60 % of patients with glomerulonephritis. In 5 children who had died from fulminant rheumatic fever the myocardium was massively infiltrated with gammaglobulin bound complement concentrated to the sarcolemma and subsarcolemma. Sowinska (289) regarded these streptococcal antibodies as specific for rheumatic fever. Besides Kaplan's streptococcal antigen Zabriskie and Freimer (380) found an antigen that cross-reacted with human heart muscle and that occurred in the cytoplasmic membrane of group A hemolytic streptococci. Other heart-reacting antibodies due to a modification of the antigenic structure of heart tissue under the influence of streptococcal toxins have also been described. In chronic rheumatic heart disease high antibody titers can persist for up to a year. Wannamaker (347) expressed the view that injury by streptolysin O may be necessary to start the rheumatic process with cross-reacting antibodies

5. Rheumatoid arthritis - factors

In our study it was of interest to find the normal frequency of rheumatoid factor.

Behrend et al. (27) studied the rheuma factor in a rural population and found a normal distribution of Waaler-Rose titers of 1:32 and above, in 4 to 6 % of normals. Tedesco et al. (327) claimed that of normal controls, 3.2 % are RA test positive and 0 % Waaler-Rose positive.

In Swedish materials the prevalence of definite plus probable rheumatoid arthritis is 3.1 % according to Hellgren (147) or 2.7 % as reported by Allander (4). Linos et al. (197), however, reports a prevalence of only 0.4 % for males and 1.0 % for females in Rochester.

F. Therapy in classical rheumatic fever

1. Pharmacotherapy

Fleischhans et al. (114) compared patients before and after the advent of penicillin and found that antibiotics radically shortened the phase of acute fever, decreased the frequency of involvement of the joints and probably also of involvement of the heart. This may, however, be due also to the previously mentioned milder course of rheumatic fever.

Nair (229) claimed that persisting tachycardia was best treated with beta

blockers. Kusakawa et al. (185) reported a good effect of early steroid therapy of rheumatic carditis. Oshima (242) also found that early administration of adequate amounts of steroids appeared effective to reduce the incidence of permanent heart defects. Wilson and Lim (362) found 7 days' treatment to be effective. The Rheumatic Fever Working Party (218, 219), however, found no difference in effect between steroids and aspirin.

2. Tonsillectomy and vaccination

Kästner et al. (188) reviewed patients who had undergone tonsillectomy more than 10 years previously. Among those with rheumatic fever, he found no effect of the operation on the course of joint involvement and the development or course of rheumatic heart disease. Early tonsillectomy immediately after the first attack, however, reduced frequency of recurrences. Bläker (40) expressed the view that tonsillectomy is superior to antibiotic therapy.

Massell et al. (212) vaccinated 21 healthy children of patients with rheumatic fever with type 3 streptococcal M protein. They concluded that such treatment can alter the patient's tissue response to later streptococcal infections in a negative way and that such vaccination should be refrained from. Fox et al. (116) immunized 51 children with a purified streptococcus type 12 M protein. Sixty per cent produced type specific antibodies, but they made no attempt to assess the prophylactic effect of the response. Taranta and Gordis (323) and an anonymous author (11) of an article in JAMA questioned the value of streptococcal vaccination and reported immunological cross-reaction between streptococcal vaccine and human heart.

3. Prophylaxis

Strasser and Rotta (308) published a report of WHO's activities, which started with the recommendations of an expert committee for the prevention of rheumatic fever in New Delhi in 1966, a seminar in 1968 and a meeting in Cairo in 1972. Efforts were made to design pilot programmes in different countries. Since 1966 WHO has had an international reference centre for typing streptococci at the institute for hygiene and epidemiology in Prague. Markowitz and Denny (205) also described the programme of the American Heart Association for primary and secondary prevention. Strasser (307) summarized WHO's present active preventive measures.

Eström (92) recommended as early as 1953 the use of penicillin prophylactically for at least 2 years in all people with rheumatic fever. Hassell and Stuart (142) also reported good results with secondary prophylaxis with long-acting benzathine penicillin. Vaccaro and Ramenghi (338) gave a survey of various

antibodies. Feinstein et al. (105) compared oral penicillin with monthly doses of long-acting penicillin injections and found the frequency of recurrences after the latter to be clearly lower. Taranta et al. (324) stressed that despite continuous antistreptococcal prophylaxis, streptococcal infections occurred in 285 patients and clear recurrences in 47 during 1 681 patient years. The frequency was higher among patients with heart disease and among those who had had several previous attacks. Wood et al. (372) used Sulfadiazin, penicillin G and benzathine penicillin with success. Shulman and Ayoub (282) recommended prophylactic treatment with penicillin in socio-economically weak groups. Berk and Canete (29) reported a good prophylactic effect of penicillin in Hawaii. Oda (237) reported no recurrences at all among 110 Japanese patients treated prophylactically with oral penicillin. Homma et al. (155) found no difference in effect of treatment with daily doses of 200 000 and 600 000 units. Since active carditis has been shown to be capable of existing up to the age of 50 to 60 years they recommend prophylactic treatment with penicillin for the rest of life. Strangely enough, Feinstein et al. (106) found no difference in effect between penicillin G and placebo.

An anonymous author (12) in the New England Journal of Medicine wondered how long prophylaxis should be continued. Shiokawa (280) claimed that it was difficult to eradicate streptococci. Johnson et al. (163) reported a series that had not received prophylaxis. Of 193 streptococcal infections, 78 % were asymptomatic and had therefore not been treated.

Taranta et al. (322) gave priority to the prevention of recurrences in patients with known rheumatic heart disease, especially children and youths and parents who had had an attack within the previous few years. Denny (84) also recommended antibiotic prophylaxis of bacterial endocarditis in patients with rheumatic heart disease and after surgery for congenital heart defects.

Dönhardt et al. (87) pointed out that side effects of chemoprophylaxis with benzathine penicillin are rare. Daikos and Weinstein (82) reported an anti-bacterial bacteriostatic antibody in patients with beta-hemolytic streptococci. It was suppressed by penicillin administration to the patients.

Gordis and Markowitz (131) stressed that streptococcal infections were no longer treated effectively, and Krause (181) pointed out that youths often do not strictly observe the doctor's prescriptions. An anonymous author (14) underlined the importance of a more detailed programme for the care of high-risk children, and Taranta (320) claimed that even patients who have had rheumatic fever earlier not infrequently discontinue the prophylaxis prescribed. He also showed that of 9 044 college students with a history of rheumatic fever or rheumatic heart disease, only 12.2 % were continuing prophylaxis. Gordis et al. (130) found it difficult to follow up all the patients in a register for prophylactic treatment.

In Malmö the rule has been to give penicillin to all patients with a history of rheumatic fever for one to two years and every time they afterwards have an attack of angina tonsillaris.

Summing up, in poor countries intensive prophylaxis is often used as far as the economy allows because of the high frequency of streptococci and of cases of VOC in patients with rheumatic disease in their history. In richer countries, especially in Europe and the USA, the disease runs a milder course, possibly thanks both to the prophylactic use of penicillin and better socio-economic standards. But it is becoming increasingly difficult to improve prophylactic methods, to keep a proper control of the patients and to follow up the patients properly. It does not appear possible to eradicate streptococci from the human environment.

G. Other microorganisms causing heart damage

1. Virus and endocarditis

An anonymous author (13) of an article in *Lancet* as well as several other investigators have stressed that nowadays many young women with mitral stenosis have no earlier history of rheumatic disease. Virus is believed to be a cause of the stenosis. Naumann et al. (231) reported that myocarditis can be caused by Coxsackie B 2, B 3, B 4, B 5 and B 6 as well as by Coxsackie A 1, A 4, A 9, A 16 and A 23 and parotitis, measles and chicken pox. Kelle et al. (174) pointed out that myocarditis can be caused by the viruses of epidemic hepatitis, mononucleosis, influenza A and B, poliomyelitis, psittacosis virus, adeno, LCM-virus and ECHO-virus, but at the same time stressed that the myocarditis due to Coxsackie virus is more severe. Burch and Giles (51) reported rheumatic heart disease due to rubella. Burch et al. (53) showed that mitral stenosis occurs in monkeys inoculated with Coxsackie virus and that the animals then have Coxsackie in the valves, endocardium, myocardium and pericardium. His group (54) also showed that acute valvulitis often developed after mass inoculation with Coxsackie B 4. Also Smith (287) reported involvement of the heart in infection with Coxsackie virus. Pearche (246) found virus 3, vaccinia, pseudorabies and inflammatory fibroma virus to cause valvular disease in rabbits. Novikov and Stulova (234) stressed Coxsackie virus cardiotropism. Sun et al. (311) described the development of mitral stenosis in *Cynomolgus* monkeys infected with B virus. They also found Coxsackie B virus antigen in a number of human hearts at routine biopsy. Burch et al. (53) studied hearts post mortem and found Coxsackie B virus in the myocardium as well as in mitral valves. Other authors have claimed ECHO 3, 6, 7, 8, 9 and 22 to injury the heart. According to Burch, steroids inhibit the synthesis of interferon and increase the virulence of the disease and should be regarded as contraindicated. Coxsackie virus particles gather along the sarcoplasmic reticulum

in the heart muscle and Coxsackie virus is also thought to be capable of causing congenital heart disease. It is suspected that virus can initiate an autoimmune reaction. Infection with rubella virus in the uterus can, according to Burch et al. (52), cause later heart disease and streptococci might be able to act as factors conditioning for cardiotropic virus. Sainani et al. (265) reported patients with heart disease and serological titers for Coxsackie B 1, B 2, B 3, B 4 and B 5. Follow-up showed that persistent heart defects, ischaemic heart disease and mitral insufficiency had occurred.

2. Ornithosis

Ornithosis has been discussed as a possible cause of rheumatic fever. Levison et al. (195) described 2 cases of psittacosis endocarditis and published a further 5 reports of all together 7 cases. Grist and McLean (134) published 2 cases of heart disease in patients with psittacosis. According to Ward (350), many of the patients with valvular lesions without a history of rheumatic disease have been in contact with birds and according to 12 different reports, psittacosis virus can cause valvular or endocardial injury.

H. Cause of heart injury

Taranta (321) discussed 3 relatively old reports in which streptococci had been found in the heart, but ascribed the findings to contamination at autopsy. Cross-reaction between streptococci and human heart has been described as a cause in practically all later investigations. Goldstein et al. (127) showed that polysaccharides from group A streptococci in animals can induce the production of antibodies, which later react with the animals' own valve glycoprotein. Hasonova et al. (140) studied heart antibodies cross-reacting with streptococcal membranes. Antibodies in patients with rheumatic fever were clearly capable of cross-reacting with streptococcal A membranes. Kaplan and Meyeserian (171) reported that the antibodies are both of 7S and 19S classes and react with various components of the myofibers. Bound gammaglobulin was localized mainly to the sarcolemma, subsarcolemma, sarcoplasm in myofibrils and vessel walls and showed signs of a histochemical change characterized by fibrinoid. Kaplan (169) found the cross-reacting antigen in cell walls of streptococci. Zabriskie and Freimer (380) showed that antisera against a large group of various serological types of group A and A variant streptococci contain antibodies that react with the skeleton, heart muscle and smooth muscle in the endocardium. According to these authors the protoplasmic membrane of the cells is the site of the antigenic determinant of group A streptococci.

Kaplan et al. (170) found serological reactions, especially in sera obtained from rheumatic patients about 2 weeks after heart surgery. Zitnan and Bosmansky

(381) stressed that antimyocardium serum factors are specific of rheumatic fever, but that antibodies in rheumatic fever, in contrast with those in other diseases, react also to streptococcal antigen. Bywaters (59) reported that the decrease in the occurrence of rheumatic fever after streptococcal infection from formerly 3 % to less than 0.3 % was due to delayed hypersensitivity, which could be prevented if the initial streptococcal infections were stopped within the first 9 days.

Baggenstoss and Titus (21) claimed that autoimmunity in rheumatic fever is due to the breakdown of normal barriers (circulation, cell membranes) that isolate the potentially antigenic substances from the circulation or immune system. They also discussed a possible ability of foreign protein as a carrier together with the host protein as haptene to form a complete antigen. An auto-immune correlation between streptococci and heart tissue was therefore thought to explain valvular injury after rheumatic fever.

III. Rheumatic heart disease, epidemiology

A. Frequencies

The frequency of rheumatic valvular disease has been the subject of many studies in practically all parts of the world. At 1 000 autopsies performed in Lund in 1934-51, mainly before the penicillin era, Edström and Gedda (93) found rheumatic heart lesions in 3.7 %. During that period the annual frequency was largely constant. In 3.5 % of the cases the lesion had been directly or indirectly caused by rheumatic fever. Of the lesions, 87 % were seen in the mitral valves, 51 % in the aortic valves, 7 % in the tricuspid valves and 1 % in the pulmonary valves. In only a few was there clinically pure mitral stenosis. Waaler in Norway (341) reported rheumatic heart lesions in 4 % of all autopsies during the period 1941-55. Anschütz and Wipperfürth (15) reported that the number of patients with rheumatic valvular disease in Darmstadt showed a tendency to decline slightly, but that the age at onset had increased from 32 in 1946 to 58 in 1968.

Yodfat (378) reported that in Israel rheumatic heart disease was less prevalent among women who had immigrated from eastern Europe than among those who had come from Asia or Africa. Of the men, the highest frequency of rheumatic heart disease was found for those born in northern Africa and the Middle East. The total frequency of rheumatic heart disease was 17 men and 26 women per 1 000 inhabitants.

Quinn et al. (256) in Nashville studied the death certificates giving rheumatic heart disease as the main cause of death and found that the mortality among blacks had decreased to one third or one fourth but only to one half in whites. The frequency of deaths among coloured and white women, aged at least 30 years,

increased from 1940 to 1965, after which it decreased. Quinn and Quinn (255) found that the mortality from rheumatic heart disease in New Haven was decreasing in the 2-24 year age class in 1920-48.

Rotman et al. (263) claimed that aortic stenosis was mostly congenital, while combined defects were most often of rheumatic origin, and aortic insufficiency of varying origin. Also Eliot (96) thought that it was time to consider the possibility of alternative origins of the heart lesions. A series of investigations have been carried out in Denver and in San Luis Valley in Colorado under the direction of Morton. In 1967 Morton et al. (225) in Denver found a prevalence of 1.7 cases of rheumatic heart disease per 1 000 school children examined. Of the children studied, 12.4 % had had rheumatic fever. The corresponding figure of rheumatic fever for those with heart disease was 44.8 %. In San Luis Valley Morton and Lichty (226) and Morton et al. (227) reported that the people were poorer than those in the rest of the state and found 3.7 cases of rheumatic heart disease per 1 000 inhabitants in 1965.

Garçia-Palmieri (119) compared the frequencies of rheumatic heart disease in various parts of the world. The frequency of rheumatic heart disease as a cause of death was relatively high in Minnesota, Spain, Costa Rica and Puerto Rico, but low in Ceylon, South Africa, Uganda and Singapore. But the pattern of the disease appeared to be the same in all the countries. Hassell et al. (141) reported a frequency of only one case of rheumatic heart disease per 1 000 inhabitants in Barbados. McLaren et al. (217) examined 12 060 coloured children in Soweto in South Africa and found the prevalence of rheumatic heart disease to be 6.9 per 1 000 and the sex ratio of men to women was 1.6:1 and mitral regurgitation was noted in 93 % of the patients. Spodick (293) underlined the large number of young coloured patients in South Africa with complications of rheumatic heart disease and Shaper (275) stated that in Johannesburg rheumatic heart disease was much more common among the coloured than among the whites. He also pointed out that in Jamaica, Jerusalem and India the picture was the same, with many children with chronic lesions of the valves. Rheumatic heart disease in early life is also common in Uganda. Ilyas (159) studied 5-15 year old children in Pakistan and found rheumatic heart disease in 18.4 % of the children. Roy (264) reported that of 25 000 patients with heart disease in New Delhi, the condition was of rheumatic origin in 32 %. Padmavati (245) stated that chronic valvular disease was responsible for the greatest number of cases of heart disease in 10 of 16 Indian states, but that only 30 % had a history of acute rheumatic fever. Nair (230) of Kerala in India reported rheumatic heart disease with a frequency of 8.5 per 1 000 children in urban schools. Joorabchi et al. (166) examined 10 676 school children in Iran. The prevalence of rheumatic heart disease was 3.5 per 1 000.

According to Bing (32); rheumatic fever in Djakarta was still the chief cause of heart disease in the lower income groups. Lue et al. (199) gave the prevalence of rheumatic heart disease in Taiwan as 1.3 per 1 000 inhabitants 0 to 9 years of age and of 1.5 per 1 000 over 10 years. Among the Chinese in Hong Kong Wu (375) found that rheumatic heart disease was the cause of 1.24 % of all deaths.

Takashina et al. (317) in Japan found in 1969 that the frequency of rheumatic heart disease in different areas of Osaka ranged from 0.02 to 0.14 %. Hirokawa and Takao (151) claimed that the prevalence of rheumatic valvular disease during 18 years had fallen from 17.82 in the beginning of the study to 4.61 % in 1975.

Setty et al. (274) reported from Bangalore that the clinical and pathological feature of the disease there differed from those in the temperate zones in that they were more common in the lower age groups, auricular fibrillation and recurrences of rheumatic fever occurred early, the morbidity and mortality were higher, and involvement of the aortic valve was less common. Hanafiah (137) found 0.3-0.8 o/oo of rheumatic heart disease in Indonesia and stated that one fifth of the cases of heart disease in Indonesian hospitals were of rheumatic origin. Hong (156) of Korea found chronic rheumatic heart disease in 0.3-0.8 % of hospitalized patients.

Mahajam et al. (201) reported that of patients with rheumatic heart disease, 52.8 % had earlier had rheumatic fever or rheumatic heart disease. Toh (333) of Singapore concluded that in patients below 20 years mitral stenosis was predominant. Kitada et al. (177) found the prevalence of rheumatic heart disease to have decreased considerably during 1958-70, while it had previously, if anything, been increasing. Valvular lesions without previous rheumatic fever had become more common also in Japan.

The difference in mortality from rheumatic heart disease between socio-economic levels tends to decrease substantially with increasing age according to an anonymous article (10). In the lower age classes the mortality is lower among the whites than among the coloured, but in the higher age classes the situation is the reverse. That the frequency of rheumatic heart disease tends to be lower among the higher socio-economic classes has been shown by among others Quinn et al. (256), Quinn and Quinn (255), Morton et al. (227), Padmavati (245) and Takashina et al. (317). According to Morton and Lichty (226), however, it is not familial poverty but national poverty that increases the risk of rheumatic heart disease in a given population. Prasad (252) reported that 32-50 % of all cases were familial. The female: male ratio of rheumatic valvular disease is generally given as 1.6-2:1.

B. Rheumatic heart disease - natural history

1. Course

The literature has been surveyed by e.g. Waldmann (343), who gave a comprehensive review of rheumatic myocarditis and its course. Wilson and Lim (361) followed a large series of children from 1916 to 1956 at the Cornell University in New York. Permanent heart injury was closely related to the incidence of acute carditis during childhood. In long term follow-ups increasing involvement of the heart was noted even in the absence of recurrent carditis. After the age of 20 the frequency of recurrent carditis was recorded as less than 3 % of the patients. By 20 years of age the anatomic diagnosis had been confirmed in practically all of the patients. More than half of them had mitral insufficiency, one third mitral stenosis and insufficiency and one eighth had combined lesions of both aortic and mitral valves. The diagnosis of mitral stenosis was firm in 79 % within 1-2 years. The mortality rate was 8.3 per 1 000 against normally 3.1. Feinstein et al. (108) reported that all patients who were free from carditis, were also free from rheumatic heart disease at review several years later, while of 260 patients with different forms of carditis, 147 had persisting heart lesions at the review. McKee et al. (216) reported the Framingham study in which 5 192 persons were reviewed after 16 years. Within this period 142 had shown clear signs of heart lesions. In 21 % the changes were due to earlier rheumatic heart disease. Waaler (342) reported that in chronic rheumatic heart disease a history of rheumatic fever was more common among men than among women. The mean age at death of those patients in his material who had died was 52.5 years. The mean interval between the first attack of rheumatic fever and death was 31 years. He also stated that in children and teenagers the course of rheumatic heart disease was more serious than among adults. According to Sanner (267), aortic stenosis has the worst prognosis with a risk of sudden death, while among those with a defect of the mitral valve, the ones with coexisting aortic lesions have the gloomier prognosis.

Spagnuolo and Feinstein (290) studied 90 episodes of cardiac insufficiency in children and youths with rheumatic heart disease without ongoing activity. They pointed out that heart lesions could occur in teenagers with rheumatic heart disease without ongoing rheumatic activity.

For 6 years Escudero et al. (100) studied 100 patients with rheumatic heart disease for which they had not been accepted for surgical treatment, 13 had died and 17 were in a bad condition. The general course in these patients appeared to be probably better than it would have been if they had been operated upon. Markowitz and Gordis (206) found that the mortality from rheumatic heart disease in USA had fallen, but not so much as that from rheumatic fever.

For 7 years Rotman et al. (263) followed 158 patients with aortic disease. Angina pectoris was more common in patients with stenosis and combined lesions,

while heart failures were more common in association with insufficiencies. The patients survived, on the average, 4 years after the appearance of symptoms.

Christian (69) described coexisting progressive endomyocardial fibrosis in rheumatic heart disease. Both conditions had the same age distribution as rheumatic heart disease. Coburn and Cone (70) reported a patient who had survived many severe rheumatic attacks accompanied by acute chronic heart disease followed by long periods of extreme cardiac incompensation, but who when last seen at the age of 52, the patient was in excellent health.

2. Time course

Natural history

Selzer and Cohn (273) stressed that it is difficult to form an opinion of the natural history of rheumatic heart disease because the indications for treatment are so strong. The traditionally reported interval of 2 to 8 years between the first attack of carditis and a firm diagnosis is surely underestimated, and they pointed out that in Bland and Duckett Jones' (39) follow-up almost two thirds of those who had mitral stenosis at the end of the study had not had any such condition at the 10 year review. Olesen (239) studied 271 patients with isolated mitral stenosis, 21 with clinically probable mitral stenosis and 59 patients with mitral stenosis combined with an aortic lesion. The patients were examined in 1933-49 and reviewed in 1951-53. Only 94 were still alive at the time of the review. The material originally consisted of 194 women and 77 men with an average age of 41.6 years when first seen. Fifty-nine had had rheumatic infection and the average interval between the first heart symptom and first observation of a lesion was 25.4 years. The average age at which the first symptom of heart disease appeared was 31.2 years, 57 % of the patients had arrhythmia, and 25 % had right-sided cardiac insufficiency. Most had enlargement of the heart, 20 % had had pulmonary infarction and 28 % had had arterial emboli in the general circulation. The average age at the time of the first attack of embolism was 45.2. Of the women, 65 % had been pregnant, and in one fourth the heart disease had become worse after pregnancy. Olesen was of the opinion that patients in function group II according to the New York Heart Association (77) with sinus rhythm have a very good median survival (over 20 years), while female and male patients in function group III with sinus rhythm have a median survival of 7-8 years and 5-6 years, respectively. The average survival after the appearance of heart symptoms was 14.3 years for 181 dead, and 20.5 for 86 still alive.

Operated cases

Klein and Klein (178) have observed reactivation of the rheumatic disease after operation on the mitral valve. It occurred in 23.3 % of the cases. It responded

to steroid and antibiotic therapy. Wood (373) found a mean interval of 19 years between rheumatic fever and mitral stenosis, but in poor areas mitral stenosis appeared to progress rapidly and to produce symptoms early. The number of operations on the mitral valve in patients below 20 years was small in USA and Italy, fairly large in Israel, and large in India and Iraq. Reichet et al. (257) from Pennsylvania stated that clinically manifest mitral stenosis can occur already within 2 years after rheumatic fever but, as a rule, takes 10 years to develop and 20 years to be symptomatic. The onset is therefore usually in the third and fourth decade of life. Elderly patients with mitral stenosis rarely had a convincing history of acute rheumatic fever since an earlier attack might not have been diagnosed or have been forgotten. Only 6 % of the patients who died from an anatomically isolated disease of the aortic valve had a history of rheumatic fever and more than half of such patients had a congenitally bicuspid or unicuspid aortic valve. Tricuspid stenosis is thought to argue for coexisting mitral stenosis.

Takeda et al. (318) claim that the duration of survival of those with aortic stenosis is 2.8-4.4 years after the onset of symptoms. Rotman et al. (263) are of the opinion that isolated aortic stenosis is usually congenital, while combined aortic defects are usually of rheumatic origin. Spagnuolo et al. (291) described 174 young patients with aortic insufficiency followed up for 10 years; 87 % had died or developed heart defects and angina within 6 years. Cullhed (79) studied the hemodynamics in isolated stenosis. All the patients with severe disability had a moderate to high pressure gradient. In Persson's (248) thorough study of aortic valvular disease a valuable hemodynamic exercise test produced information for predicting the subsequent course in aortic valvular disease. Helfant (146) found that isolated valvular aortic stenosis is commonly congenital and is generally diagnosed before the age of 30. Patients with aortic stenosis of rheumatic origin developed symptoms in middle age. Degenerative aortic stenosis is the most common cause of aortic stenosis after 75 years of age, but rarely manifests itself before the age of 65. Ebert (88) stressed that bacterial endocarditis is a common cause of aortic regurgitation. Syncope occurs in 80 % of all patients with aortic stenosis, but aortic stenosis per se does not always increase the incidence of coronary arteriosclerosis.

Acquired tricuspid stenosis or insufficiency most often follows rheumatic fever or carcinoid. Thorson and Waldenström (329) have given an excellent review of the tricuspid lesions of 66 patients and discusses its connection with 5 HT and its precursor. Pulmonary disorders are, as a rule, congenital.

C. Pathology of the valves

According to Jansen (160) the primary and most frequent point of attack seems to

be the endocardium while the myocardium is left until later or not at all. The prototype of a late allergic hyperergic reaction of the heart valves and heart muscle, in the form of a late reaction is rheumatic endocarditis and myocarditis. Chronic fibrotic endocarditis is the more common. It is not known whether the endothelial injury is primary or secondary. Cosh (72) claims that pericarditis often appears as the first sign of rheumatic fever and that the myocarditis is characterized by Aschoff bodies. In the acute stage, endocarditis causes thickening of the mitral and aortic valves and the formation of small vegetations on the contact borders of the valves. Oedema of the cusps is followed by capillary vascularisation, lymphocytic infiltration and later by an increase in the fibroblasts. During the following years the adhesion advances slowly and leads to stenosis. Sometimes the thickening is predominant which contraction of the cusps and chordae tendineae with incompetence as a result. Valvular injury involves the mitral valve in 85 %, the aortic valve in 45 %, and the tricuspid valves in 15 %.

Bailey et al. (22) reported the findings in heart biopsy specimens. In patients with function grade I the myocardium was usually normal, in grade II there was advanced fibrosis and loss of muscle mass.

Biörck et al. (34) reported 18 patients operated upon for mitral stenosis with congenital anomalies but free from rheumatic activity, and felt that there might be continuous progression of rheumatic activity without demonstrable acute exacerbations or increase in positive laboratory tests of ASL type. In biopsy specimens of the left atrium obtained in association with mitral valvotomy Malik (202), Misu (223) and Enticknap (98) often found Aschoff bodies in clinically inactive cases.

Roberts (259) claimed that while mitral adhesions are most often of rheumatic origin, one should also make a search for other possible causes of aortic lesions. Edwards (94) thought that as far as calcifying aortic stenosis is concerned, it is then a bicuspid aortic valve that is responsible for the deposition of calcium. Two main conditions lead to calcifying aortic stenosis, namely rheumatic endocarditis with fusion of two of the three cusps and congenital anomalies.

1. Rheumatoid arthritis and valvular defects

Rheumatic fever and rheumatoid arthritis are believed to be two different entities. Valvular injury has, however, been reported in rheumatoid arthritis. Bonfiglio and Atwater (44) claim that in seropositive rheumatoid arthritis there are sometimes granulomatous valvulitis and valvular insufficiency. Carpenter et al. (61) reported a case of rheumatoid arthritis and rheumatic nodules in all four heart valves.

D. Clinical evaluation

1. Roentgenology

In Sweden the size of the heart is measured with Jonsell's method (164), and this was used by us.

Filming of the heart (cine-cor) is reportedly a valuable method for judging, among other things, the presence of valvular calcification and function of a prosthesis. Freundlich (117) expressed the view that endocardial calcification is mostly the result of rheumatic heart disease. He found that the incidence of atrial calcification in mitral disease is 9.5 %, and calcification of the heart valves argues for previous rheumatic disease. The mean age of the patient at diagnosis of calcification in congenital aortic stenosis was 28 years, in rheumatic aortic stenosis 47 years, and in arteriosclerotic valvular degeneration 54 years. In Wood's (374) investigation calcification of the mitral valves was practically always secondary to rheumatic valvulitis.

2. Digitalis levels

The method we used for measuring the level of digoxin has been described by Thorell and Larsen (328), Oliver et al. (240) and Hoeschen and Proveda (152). Hayes et al. (143), however, underlines that it is difficult to distinguish between intoxicated and non-intoxicated patients, even though the mean blood concentrations of the drug are higher in the former group. Landahl et al. (191) found in 70-year old inhabitants of Gothenburg that in only 60 % of those treated were the serum digoxin within the therapeutic level. Of the 13 % of the population with an indication for digitalis, 25 % received no such treatment. Butler and Chen (58) have demonstrated antibodies that can bind digoxin.

E. Complications

1. Hemolytic anemia

Hemolytic anemia in valvular disease is common and is described in all textbooks. Brodeur et al. (48) studied the survival of the blood cells in patients with aortic disease and various types of prostheses. The survival of the red cells was reduced in the majority of patients, and the authors suspected that such patients have a population of blood cells that undergoes rapid destruction and does not occur in normal individuals. They also found patients with a positive Coomb's test suggesting the development of antibodies against red blood cells. Hemolytic anemia is also reported in mitral lesions but in lower frequencies. Rodgers and Sabiston (260) stressed the effect of turbulence on the destruction of blood cells and recommended iron and folic acid therapy. Walsh et al. (345) stated that a low haptoglobin level and a high S-LD are good evidence of hemolytic disease and stated that strenuous physical exercise increases the hemolysis.

Anemia has also been a considerable postoperative problem owing to hemolysis due to mechanical factors of the valves and prostheses.

Henze and Fortune (148) showed, in a test chamber, that hemolysis is milder in patients with a non-overlapping disk of Björk-Shiley type than in those with an overlapping disk, such as the Lillehei-Kaster pivoting disk. Herr et al. (149) and Petz and Goodman (249) stressed that hemolytic anemia is common in leakage of valvular prostheses. Cuddigan and Speller (78) described anemia due to intra-vascular hemolysis.

2. Thromboembolism

Thromboembolism is a common complication of VOC. Coulshed et al. (75) claimed that systemic embolism is equally common in mitral regurgitation and mitral stenosis. Atrial fibrillation with the formation of thrombi in the atrium predisposes to thromboembolism, but the predisposition does not vary with the size of the auricle. Harker and Slichter (139) reported that platelets are selectively consumed by interaction with the valves and in an amount varying with the surface area of the valves. Szekely (315) found the incidence of embolism to be 1.5 % per patient year. The frequency was 7 times as high in the presence of auricular fibrillation. One third of the cases of embolism occurred within one month of the beginning of fibrillation. Hutchinson and Stock (158) found cerebral episodes in 14 % of patients with rheumatic heart disease.

Steele et al. (296) and Weily et al. (355) found an association between the shortness of the survival of platelets and the occurrence of embolism. Starr-Edwards prostheses proved to change the survival of platelets which direct homografts did not.

Kellogg et al. (175) reported that of patients who had undergone mitral commissurotomy, 28 % had embolism preoperatively, 6 % had embolism in association with the operation and the survivors had systemic embolism with an incidence of 4.8 % per patient year.

F. Therapy

1. Anticoagulation

Owren (243) recommended that all patients who have a defect of the mitral valve and who have had embolism should receive anticoagulant prophylaxis for the rest of their lives. Fleming and Bailey (115) found that in patients with a defective mitral valve, long-term anticoagulant prophylaxis reduced the frequency of embolism to less than 20 % of that expected in untreated patients. Adams et al. (3) reviewed 84 patients with mitral stenosis and cerebral embolism after 20 years. Half of them received warfarin, and after 10 years 31 % were still alive compared with 7.1 % of the untreated patients. Askey and Bernstein (17) considered the

reduction of the prothrombin to 30-50 % level to be sufficient. McDevitt (215), Wessler (359) and Siekert (284) stressed also the importance of anticoagulant prophylaxis.

Gadboys et al. (118) studied patients operated upon with implantation of an artificial valve and found that anticoagulant therapy markedly reduced the frequency of embolism.

2. Defibrillation

Grosser (135) published a careful survey of electrotherapy of auricular fibrillation and gave a list of indications and contraindications for cardioversion. Bell et al. (28) reported that of 100 patients with mitral disease, defibrillation was initially successful in 73. Åberg and Cullhed (1) treated 181 unselected patients with atrial fibrillation with defibrillation. Only 22 of those in whom treatment was initially successful showed a sinus rhythm after one year. Korsgren et al. (180) treated 138 patients and 43 % of those that responded showed a sinus rhythm after 2 months, i.e. 33 % of the entire series.

3. Operation

Heart surgery is of relatively recent date. In 1948 Glover et al. (126) were the first to describe successful operations on the mitral valve. In 1953 Wulff et al. (376) published a one-year series of operations performed in Malmö, and Björck et al. (35) reported 50 patients in whom the postoperative mortality was 14 %, but improvement in 68 % of the patients.

Björck et al. (36) and Björck et al. (37, 38) described consecutive operations on aortic lesions with the Björck-Shiley prosthesis. The durability of the prosthesis in vivo was good and the clinical improvement lasted for 5 years. Sanner (267), however, found a 5-year survival rate of only 68 % among patients with an artificial valve. As far as hemolysis is concerned, the Björck-Shiley prosthesis was better than the Starr-Edwards and Lillehei-Kaster. Starr and Edwards (295) published a series which they had treated with the Starr-Edwards prosthesis and in which they found the hemodynamic results satisfactory. Kaster et al. (172) described the advantages of Lillehei-Kaster pivoting disk. Bonchek and Starr (42, 43) and Starr et al. (294) described operations carried out in 1965-74 with the insertion of a ball valve prosthesis. Cloth-covered prosthesis and warfarin reduced the incidence of embolism. Cohn et al. (71) tried porcine aortic valve xenografts with good results despite the absence of anticoagulant prophylaxis. Brown et al. (49) compared the Kay-Shiley, Starr-Edwards prosthesis and the porcine xenograft in operations on the mitral valve and found that the frequency of complications was lowest for operations with the porcine xenograft. Pacifico et al. (244) found homografts in the aortic valve to be better than Starr-Edwards

model. O'Brien et al. (236) reported good results with heterograft valves in the aortic and the mitral valve. Finchum (112) reported an operative and late total mortality of 14 % in a mixed material of 62 acquired and 34 congenital, operated lesions. The electrocardiogram and the roentgenographic size of the heart became normal in more than 50 %. Yacoub et al. (377) described satisfactory results with unsupported homografts. Senning introduced the fascia lata graft, but found problems because of the frequent occurrence of aortic incompetence. Gonzales-Lavin and Ross (128) found treated patients with an autologous fascia lata valve having a total mortality of 23 % within 18 months.

Van der Horst et al. (157) used Starr-Edwards prosthesis and mounted an inverted homograft in 51 children with subsequent dramatic improvement in clinical status of the 44 survivors. Martelli et al. (209) reviewed patients operated upon with a homograft, a pulmonary valve autograft and a Starr-Edwards prosthesis. The results were more unfavourable in those with a mechanical graft.

John et al. (162) reported that in India, where rheumatic heart disease runs a more fulminant course, the surgical approach is much more aggressive and has produced good results in the treatment of severe mitral incompetence. Manabe (203) also described good surgical results in very young Japanese patients with mitral stenosis. Turner (334) stated that delay of operation leads to progressive complications. Lower (198) reported the results of heart transplantation in patients with not only coronary arterial defects but also advanced virulent rheumatic heart disease. He described the surgical methods used and the clinical results. Kakvan and Wright (167) pointed out that all operations for valvular disease are palliative and Munoz et al. (228) found no difference in the 5-year survival after medical and after surgical treatment of mitral and aortic defects. Kakvan and Wright (169) pointed out that mechanical failure of a prosthesis is rare.

Jonsson (165) stressed that the age limit for heart operations has risen and that today insertion of an artificial valve can be done without hesitation in patients as old as 75 years. He also stated that all patients with mitral stenosis with movable valves should be operated upon, but that a mitral prosthesis is indicated only if the patient has disabling symptoms. Mitral insufficiency is more difficult to judge, because it is not possible to measure the regurgitation exactly. Aortic stenosis with an area of 0.5 mm^2 per m^2 body surface with marked ECG abnormalities should be treated surgically even in the absence of symptoms. Aortic stenosis is thought to indicate operation even if the area is in the upper limit, if it is complicated by calcification. The Persson (248) hemodynamic exercise test discussed previously is of importance for evaluating the ideal time for operation. Acute severe aortic insufficiency indicates operation as soon as possible.

4. Operation in the active rheumatic phase

Timmis et al. (331) recommend operation on patients with a refractory heart defect and isolated valvular lesion irrespective of the activity of the rheumatic process. Strauss and Goldring (309) expressed the opinion that surgical treatment of the valves in the active phase may be life-saving in children with severe active rheumatic heart disease. Strauss et al. (310) described 4 successful operations on patients in the active stage of rheumatic fever. Gersony et al. (121) is, however, hesitant about operation in active disease.

G. Valvular disease and pregnancy

According to Krivitsky and Antonenko (182), the hormone function in the ovaries is markedly decreased in active rheumatic disease. Metcalfe (220) found the tendency to lung oedema to be increased in mitral stenosis. Emergency surgery during pregnancy is rarely indicated, and pregnancy is not a suitable time for elective heart surgery, but it may sometimes though very rarely, be necessary.

Wallace et al. (344) reviewed 139 women after, on the average, 10 years after they had undergone mitral valvular operation and later become pregnant. The post-operative course in these cases was not affected by childbirth. Of 248 pregnancies, 192 resulted in livebirths. Handjani et al. (138) studied 55 pregnant women who had rheumatic heart disease and who had been pregnant at least 5 times. There was no maternal mortality and the fetal mortality was 17.6 %. The older the women and the larger the number of previous pregnancies, the greater the risk for the child. But in many cases the number of children did not have any demonstrable effect on the late prognosis. They also felt that 98 % of heart patients who become pregnant can be expected to survive. Kiselev (176) studied the course of pregnancy and labour in 128 women receiving anti-rheumatic treatment. He found the contractile activity of the uterus to be decreased. Chesley (68) compared women with and without later pregnancies and found such pregnancies to have no negative effect on the course of the heart disease. From 1939 to 1962 (66, 67) he reviewed more than 1 500 pregnant women. Only 2 of the mothers died and none had undergone therapeutic abortion. In patients with rheumatic heart disease and who survive pregnancy the pregnancy appears to have no noteworthy effect on the course of the heart disease.

Chapter III

MATERIAL AND METHODS

I. The town of Malmö

Malmö is the third largest town in Sweden. During the present study period its population increased from 127 873 in 1930, to 209 473 in 1955 and to 265 505 in 1970 (Fig. 1). The number of children 0 to 14 years of age rose from 24 029 in 1930 to 49 328 in 1970. Thus, during the study period the total population and the number of children below 14 doubled. This was due to a rapid economic expansion. The population has since begun to decline, but children 0-15 years old still constitute one fifth of the population.

The age distribution of the population of Malmö was largely the same as that of the population of the entire country during three representative years (Fig. 2). Owing to lack of reliable statistical data, however no satisfactory figures were available until 1945. The figures for higher age groups and groups of early childhood were, however, somewhat smaller than those for the country as a whole. But the differences were by no means such as to impair the above mentioned representativeness of the population of Malmö.

Malmö has only one acute somatic hospital (Malmö general hospital), but up to 1950 it also had a small private children's hospital (Rönneholmskliniken) for minor diseases. It also has a small Catholic nursing home (Elisabethsysterns sjukhem). This children's hospital and nursing home are not included in Hall's material and therefore not in this investigation either, but the cases of rheumatic fever seen at the children's clinic are accounted for separately in the section on rheumatic fever. All the patients were treated at Malmö general hospital, Värnhems geriatric hospital, or the Eastern psychiatric hospital. Since the 40s Malmö general hospital has gradually become a university hospital attached to Lund University. Of persons seeking medical advice in the 30s, about 50 % visited the out-patient departments at the hospital, in the 60s the number was 60 %; the remainder consulted private practitioners in the town. Patients

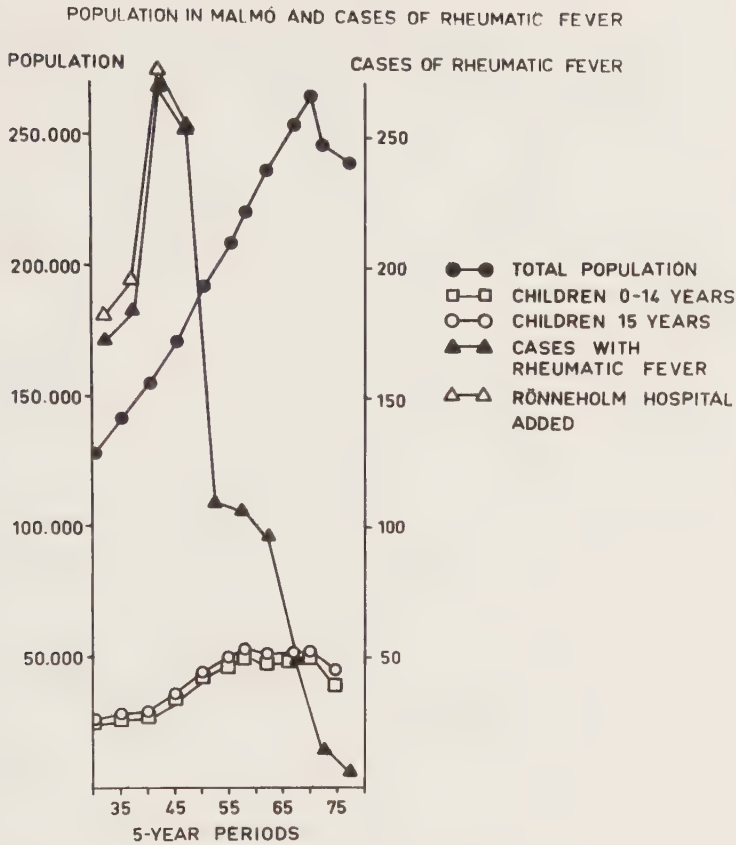


Fig. 1 Population in Malmö 1930-80 compared with cases of rheumatic fever.

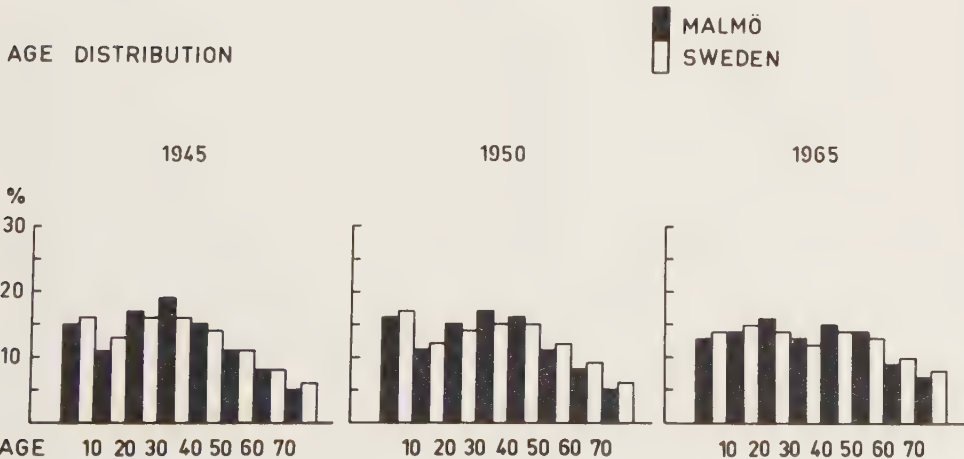


Fig. 2 Histogram illustrating similarity in age distribution between Malmö and Sweden during study period.

with rheumatic fever were regularly admitted to hospital. During the study period and up to the 60s the Swedish legislation prescribed that also patients with scarlet fever should be admitted to hospital. Malmö general hospital has served both as a primary hospital and a regional hospital, for which reason all patients were referred to this hospital for the diseases in question. Those patients who were not living in Malmö but who were referred there, have been eliminated from the material, as have those who were not living in Malmö when the diagnosis was made. The material examined may thus be regarded as representative of the population of Malmö.

II. The material

The present investigation is based on two materials, one consisting of all cases diagnosed in 1930-54 and referred to as Hall's material; and those cases diagnosed in 1955-70 and here called the author's material. In 1961 Hall (136) published a thesis "On the prognosis and natural history of acute rheumatic fever and rheumatic heart disease - a study upon a 25 year material in a Swedish town served by a single hospital". In that study he carefully searched the archives at the departments of internal medicine, infectious diseases, orthopaedics and pediatrics at Malmö general hospital for the following diseases:

1. Acute rheumatic fever including such diagnoses as acute polyarthrititis, acute endocarditis and chorea minor.
2. Rheumatic heart disease including such a diagnosis as "vitium organicum cordis", but not syphilitic heart lesions or congenital heart disease.

In 1930 to 1944 patients who died in Malmö general hospital were autopsied by pathologists from the department of pathology, Lund university. All patients from the departments of medicine, infectious diseases and pediatrics with the above diagnosis and autopsied in 1930-44 are included in the present material. In 1944 a special department of pathology was set up in Malmö. From then on it was possible to trace and include all patients who had died in the hospitals in Malmö and had any of the above mentioned diseases.

In 1971 the records were analysed for all patients who had in 1955-70 been treated at the department of internal medicine, infectious diseases, orthopaedics, pediatrics, thoracic surgery, general surgery, ear nose and throat diseases, Värnhems hospital or the Eastern hospital. In 1975, the first year in which diagnoses made in outpatients of the department were registered in a uniform way, the registers for diagnoses in outpatients were searched for conditions possibly related to the development of the above mentioned diseases in the years in question.

The diagnoses sought were:

1. Acute rheumatic fever, including such diagnoses as acute polyarthrititis, acute endocarditis, chorea minor, scarlet fever with involvement of joints and the heart and acute glomerulonephritis. Diagnoses in patients without a history of rheumatic fever were disregarded.
2. Rheumatic heart disease including not only the heart defect, but also such diagnoses as unspecified heart disease, syphilitic heart disease, Bechterew's disease and Marfan's syndrome. Cases without rheumatic heart affection or with heart disease of other origin were not included in the material. The autopsy protocols for 1955-70 were studied for the above diseases and the clinical records of the patients were analysed in the same way.

III. The review

Hall's study

In 1953 all together 1 109 patients were reviewed at the heart laboratory. Originally the purpose was to select patients for mitral surgery, but was afterwards extended to include:

1. Evaluation of the natural history of rheumatic fever.
2. Collection of information of the composition of the series with rheumatic heart disease.
3. A general pilot study of the heart in a selected group of the population.

In 1930-54 the total number of new cases of rheumatic fever was 1 434 and that of rheumatic valvular defects 1 208.

The author's study 1974

The records of Hall's 1 208 patients were studied in 1971 by the present author regarding firmness of diagnosis according to Jones' revised criteria, as judged from the hospital records and questionnaires. The composition of the material in respect of rheumatic fever is given in Fig. 3. It is clear from the figure that 268 patients did not meet the revised criteria for rheumatic fever and were therefore not invited to the review. The number that declined the invitation to an after-examination was small, namely 85 of 909. In addition, 115 had died in the meantime. As for the patients with organic lesions, only 26, sixteen belonging also to Hall's series, declined the invitation. Since a large group of the patients with rheumatic fever developed an organic heart defect during the study period, the material's overlap and some patients appear under the heading of both rheumatic fever and organic heart defect. In 1955-70 there were 245 cases of rheumatic or other valvular defects. The purposes of the present study were:

to elucidate the natural history of rheumatic fever,
 to shed light on the natural history of rheumatic heart disease,
 to study the changes in the clinical picture of acute rheumatic fever with
 time and the possible cause of them,
 to find out to what extent such changes affect the clinical picture of
 organic heart defects,
 to form an opinion of the heart status in a selection of a population, and
 to try to evaluate the effect of penicillin treatment in rheumatic fever on
 the development of rheumatic heart disease.

A. Review in 1961

In Hall's study the following methods were used:

1. Analyses of records with special reference to earlier medical and cardiologic notes.
2. Complete physical examination.
3. Laboratory studies; hemoglobin, urine, ESR, Westergren (60).
4. Electrocardiography. In 1953 three standard limb leads and a chest lead (V_4), but in 1954-59 12-channel unipolar electrocardiography.
5. Full chest X-ray, frontal and lateral, measurement of heart volume.

Supplementary examinations when indicated

1. Unipolar electrocardiography in 1953
2. Antistreptolysin titre. Agglutination of sensitized sheep cells.
3. Wasserman's test.
4. Basal metabolic rate.
5. Observation in hospital.

The examinations were free of charge for the patients. They were invited by letter to the department. In 1953 the clinical examinations were carried out by Björck, Bülow and Hall; afterwards by Hall only. Invitations were mailed to 1 322 persons, 172 (13.0 %) invitations were returned unopened and 41 (3.1 %) declined. This left 1 109 for the investigation.

B. Review in 1974

In 1974 the patients included in Hall's series of rheumatic fever were reviewed as well as the patients who had had their first attack of rheumatic fever in 1955-70 and those in whom rheumatic heart disease was discovered during the later period. The composition of the groups is given in Fig. 3. (A small group of patients from Rönneholm children's hospital was not included in Hall's material

RHEUMATIC FEVER FIRST TIME CLINICAL MATERIAL

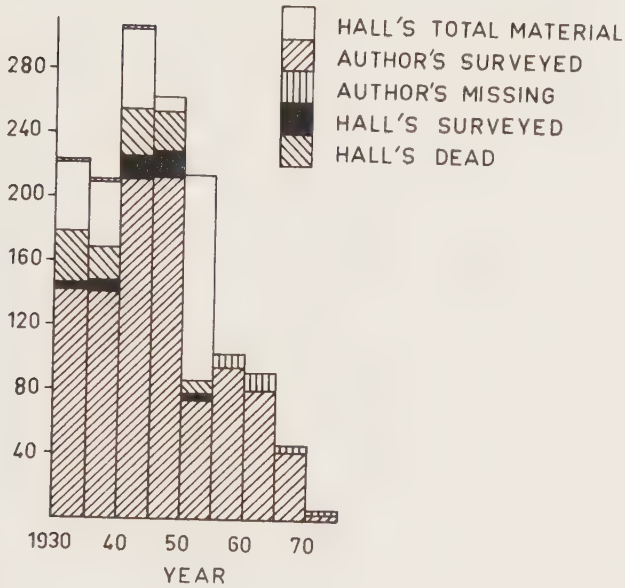


Fig. 3 Hall's total material, including patients not meeting Jones' criteria with certainty or not willing to cooperate or not traced.

Hall's material

Author's material reviewed

Author's cases missing

Hall's material reviewed

Hall's patients dead

and is not included in the present review in order not to disturb the comparability of the materials. They are instead accounted for in a later section). In 1974 the review comprised the following factors.

1. Questionnaire:

Heredity, medical history (general medicinal and cardiologic), course of disease, social factors etc. The questionnaire was discussed with the patient at a personal interview with the author.

2. Analysis of earlier hospital records with special reference to general medical, cardiologic, rheumatologic and social factors.
3. Complete physical examination. Blood pressure, right arm after 10 minutes rest in recumbent position. Height and weight.
4. ESR (Westergren) (60). Haptoglobin as measure of hemolysis (193).
5. Electrocardiography with 12 unipolar leads (I, II, III, aVF, aVR, aVL, V₁, V₂, V₃, V₄, V₅ and V₆). Also 5 minutes ECG (I, II, III, aVF, aVR, and aVL) for arrhythmia. The Minnesota code was used for interpretation of the recordings (189, 270).
6. Complete heart-chest X-ray, frontal and lateral, including determination of heart volume according to Jonsell (166). The films were examined by one and the same roentgenologist (Aspelin).
7. Cine-cor-radiography for valvular calcifications, likewise judged by the same roentgenologist (Aspelin).
8. Antistreptolysin titre according to Winblad et al. (369), evaluated by Winblad.
9. Agglutination of sensitized sheep cells (Waalser-Rose) and antigammaglobulin on latex particles (65, 364, 365, 366, 367 and 368), evaluated by Winblad.

A selection of the patients were examined with the following methods:

1. Blood samples for determination of the plasma digitalis level according to Thorell and Larsen's RIA method were obtained from all patients in the morning after overnight fast and before ingestion of the drug in all patients taking digitalis (digoxin or cedilanid).
2. The patients with rheumatic defects were arranged according to date of birth, and every fifth one was selected and examined with spirometry and blood gas analysis.
3. All the patients in whom the diagnosis of organic lesion of the heart was doubtful were check-examined by a further examiner, Johansson, and with phonocardiography and apex cardiography and sometimes also with ultrasonic cardiography.
4. All the patients with rheumatic heart disease filled in a special questionnaire concerning ornithosis and contact with various sorts of birds.

5. All patients with rheumatoid arthritis or rheuma factor were examined roentgenographically for joint and hand changes and were classified according to Mikkelsen (222). Tracing of the patients in the archives was done in 1971. In the 1973-74 winter the parish registers were examined to find out how many of the patients were still alive and how many had died. The invitations were afterwards mailed to all those still alive. The examinations were free of charge for the patients. They were invited by letter to the heart laboratory of the department of internal medicine. The letter explained the purpose of the examination and a time for the examination was suggested. Informed consent was obtained.

In 1974 invitations were sent to 909 persons, and 824 accepted. As for the remaining 85, four could not be traced, 61 refused, and 20 were abroad. Judging from available data, 49 of these 85 did not meet the criteria for a firm diagnosis of rheumatic fever. The remaining patients were reviewed and are accounted for here. Of those patients who had moved from Malmö, 54 were examined by the author at their local hospitals and 24 by well informed colleagues. All the others were examined in Malmö. All together 22 patients were later examined cardiologically to decide whether cardiologic surgery was indicated.

C. Autopsies

Of all persons who died in Malmö in 1945, 28.8 % were examined post mortem. This figure rose to 44.4 % in 1955 and to 69 % in 1961 and to 82 % in 1965. No exact figures are available for the years before 1944. Since more than half of all deaths during the study period occurred in the hospitals of Malmö, and since a high percentage of the cases were examined post mortem. Malmö is of a suitable size and offers good possibilities of ascertaining the causes of the deaths.

D. Representativity of Hall's material

Hall's study is based on 2 reviews, one in 1953 and the other in 1958.

For technical reasons he examined only about half of those who were still alive in January 1958. However, all of them had been reviewed on some occasion. In the beginning of the investigation in 1953, when the main purpose was to select patients for mitral surgery, the patients treated in 1940-49 had a better chance of being examined than those treated in 1930-39, firstly, because it was easier to trace them and, secondly, because in 1953 more time was reserved for examining the women than the men, but this had no effect on the representativity of the material studied in the present investigation.

The representativity was strengthened by a number of check studies by Hall. In 1958 all those who had had chorea and were still alive were examined, except 4 men living outside Malmö, and all those who were not examined in 1953 and who were in a good state of health. Those reviewed in 1953 did not differ in age at

the first attack from those examined in 1958. It is clear from Hall's thesis and check-ups that there was no reason to assume any difference between those examined in 1953 and those examined in 1958. The group could therefore be regarded as representative.

E. Statistics

In the present study the social structure in Malmö in 1955 was compared with Werner's (358) socio-ecological investigation of thieves in Malmö in 1963. That investigation was made at a relatively suitable time for us, i.e. in the middle of the present period. The statistical methods used in our study are described in Lund Datacentrals handbook (200).

F. Virology

Coxsackie virus can, as mentioned, be one explanation for the development of rheumatic valvular disease. This could not be studied in the Malmö material for two reasons. The condition could not be properly diagnosed in Malmö before the early 1960s and even then the frequency of viral studies was low. The serological diagnosis of Coxsackie virus was not made to any large extent in Malmö until about 1969. It was therefore not possible to assess the frequency of the disease during the present study period. Therefore no virological studies were used.

IV. Reference material

Certain problems dealt with in the present investigation, such as the frequency of rheumatoid arthritis, carditis, rheuma factor and exposure to the risk of ornithosis, required a reference material. For every seventh patient in the study in decreasing order of age a person of the same sex and born on the same day and living in Malmö was selected. Since the controls were volunteers without any special motivation, the questions posed were relatively few and brief, and the medical examination consisted only of serological studies. Of the 153 persons invited, 106 accepted. The remaining 47 persons were mainly in the lower age groups. The loss did thus not imply any effect on the age distribution of the control series with a shift towards healthier groups.

Anamnestic questions in the reference material

Only 3 of the controls had had rheumatic fever. None of them had the disease in Malmö in 1930-70. None had had any known valvular defect, while 3 had chronic rheumatoid arthritis, a number agreeing well with that found in large population studies, 18 controls had had scarlet fever. One had had erysipelas, and one had had chorea, but not had the attack in Malmö in 1930-70. None had to their knowledge had carditis, and only 6 reported that they had some unspecified

heart or joint disease.

Serology in the reference material

Only 2 of the controls had positive sensitized sheep cells (SSC) and 2 a positive acryl fixation test. In one of these controls both SSC and the acryl fixation tests were positive.

V. Composition of rheumatic fever series reviewed

The materials studies is summarized in Fig. 3. The number of non-participants was small (5 %). Those parts of the columns denoting patients included in Hall's total material consisted of patients whose records did not contain sufficient evidence for a firm diagnosis of rheumatic fever or in whom the symptoms afterwards proved to be of some other origin, such as early rheumatoid arthritis. The same modification of Jones' criteria were used, as in Hall's study, though probably, above all, the criterion arthritis more strictly in the present investigation; and that may therefore explain the difference in accepted patients throughout the whole 1930-54 period. In the present study the criteria were identical over the whole 1930-70 period and the trends should therefore be correct.

All the cases of rheumatic fever in 1930-70 were reviewed. But the cases from Rönneholm children's hospital were studied in less detail because they were not included in Hall's material. This also applies to the frequency of rheumatic fever in 1970-75. Since Hall had described the manifest valvular defects up to 1955 the present investigation of valvular defects was started that year. On the other hand, all patients who had had rheumatic fever in 1930-70 were reviewed for heart defects.

CHAPTER IV

CLASSIFICATION

I. Acute rheumatic fever

A. Criteria

In 1944 Duckett Jones (85) published his classical study of the criteria for rheumatic fever. They have since been modified by the Committee on Standards and Criteria for Program of Care (5), and this was used with the later following modifications in Hall's and our investigation. The criteria were again revised in 1956 by The American Heart Association (6) and in 1965 by Stollerman et al. (303). But the differences between these classifications are small and imply only that more importance was ascribed to the role played by streptococci and to tests for streptococci. In the present investigation Hall's modification was strictly adhered to in order to make his and the author's investigations comparable and not to disturb the material. The criteria have, however, been criticized. Thus, Feinstein et al. (109) stressed the difficulty in diagnosing borderline cases. Cossermelli and Pastor (73) also found the classical criteria difficult to apply. Davis (83) expressed the view that the most important criteria are those for carditis and chorea and that migratory polyarthrititis is a supportive sign, while nodules and erythema marginatum are non-specific and rare.

The criteria from AHA 1955 are designed only to guide the clinician towards a diagnosis of the disease and to distinguish this disease from others and to restrict the diagnosis of rheumatic fever to illnesses with acceptable criteria.

B. Criteria for rheumatic fever in our study

In our study and Hall's study the following criteria are used.

Major criteria

Carditis

Subtaneous nodules

Polyarthrititis

Erythema marginatum

Chorea

Minor criteria

Fever

Preceding beta hemolytic streptococcal infection

Arthralgia

Prolonged PR-interval in the ECG

Previous rheumatic fever or inactive rheumatic heart disease

Increased ESR or presence of C-reactive protein, or leukocytosis

1. Major criteria

Carditis

Carditis, as evidenced by one or more of the following changes:

Murmurs

(a) A significant apical systolic murmur, apical mid-diastolic murmur, or basal diastolic murmur in an individual without a history of previous rheumatic fever or in whom there is no reason to assume pre-existing rheumatic heart disease.

(b) A change in the character of any of these murmurs during observation of an individual with rheumatic fever. (c) Roentgenologically manifest advancing cardiac enlargement.

Pericarditis

Pericarditis manifested by a friction rub, pericardial effusion, or definite electrocardiographic evidence.

Congestive failure

Congestive failure (in a child or young adult under 25) in the absence of other manifest causes.

Polyarthritiis

Polyarthritiis tends to be migratory and is manifested by pain and limitation of active motion, or by tenderness, heat, redness, or swelling of two or more joints. Arthralgia alone, without objective evidence of joint involvement is not a major manifestation.

Chorea

This must be differentiated from habitual spasm, athetosis, and cerebellar ataxia. Movements must be characteristic, involuntary and of moderate severity if chorea is to be used as a major manifestation.

Subcutaneous nodules

These are shot-like, hard bodies seen or felt over the extensor side of certain

joints, particularly elbows, knees, and wrists, in the occipital region, or over the spinous processes of the thoracic and lumbar vertebrae.

Erythema marginatum

This recurrent pink, characteristic rash of rheumatic fever, in which the colour gradually fades away from its sharp scalloped edge, is found mainly over the trunk, sometimes on the extremities, but not on the face. It is transient - is brought out by heat and migrates from place to place.

2. Minor criteria

Fever

A significant rise in temperature is a common symptom, but as it occurs in so many illnesses, it has little differential diagnostic value. In order to be included, the elevation of temperature must clearly exceed the normal diurnal fluctuation, which may vary widely from individual to individual.

Arthralgia

Pain clearly located without objective findings is only a minor criterion for diagnosis. The pain must be in the joint, not in the muscles or other peri-articular tissues, and it must be distinguished from the nocturnal pain in the extremities occurring in normal children. Arthralgia must not be used as a minor criterion when polyarthritis is included as a major one.

Prolonged PR-interval in the electrocardiogram

Prolongation of the PR-interval may be non-specific; it is considered a minor criterion and is not diagnostic of carditis. It cannot be used if carditis is already included as a major manifestation.

Increased erythrocyte sedimentation rate, presence of C-reactive protein or leukocytosis

One or more of these non-specific signs may be considered as a single criterion. Particularly to be deplored is the tendency to use any of these tests as a major criterion or as diagnostic of rheumatic fever.

Evidence of preceding beta hemolytic streptococcal infection

This must be documented by a history of scarlet fever or by a typical clinical picture of another streptococcal infection preceding the onset of rheumatic fever by one week to one month, the nature of the infection being confirmed by a history of immediate contact with other individuals having typical streptococcal infection, or by positive culture of material from the nose or throat in which

beta hemolytic streptococcus predominates, or by an elevated or rising anti-streptolysin-O titre.

Previous history of rheumatic fever or the presence of inactive rheumatic heart disease

The existence of either of these may be used as a minor criterion in deciding the rheumatic nature of the illness in question, but only if the previous history can be documented by the same objective criteria as are set forth in this statement or by the presence of inactive rheumatic heart disease.

According to the criteria set up by the American Heart Association, the presence of two major criteria or one major and two minor criteria indicates a high probability of the presence of rheumatic fever.

3. Comments

In order to secure uniform criteria for the material, which dates back to 1930, it was found necessary to modify the criteria of the AHA in a few respects.

The conception of the significance of an apical systolic murmur has changed in the course of the last years, and the present definition of an organic mitral murmur as a pan-systolic apical murmur audible out in the left axilla differs from that in the beginning of the period covered by the present investigation. Since it was not possible to evaluate the significance of the murmur from the hospital records, it was necessary to rely on the opinion of the clinician. A systolic murmur per se in patients with acute rheumatic fever was not accepted as a sign of acute endocarditis, except in a few cases, in which a systolic murmur developed while the patient was under observation.

During the years 1930-44, laboratory facilities were limited; therefore it was not possible to culture throat swabs or determine the antistreptolysin titre in suspected cases of rheumatic fever. If a patient had tonsillitis before admission, it was regarded as a minor manifestation even if the tonsillitis could not be related with certainty to previous streptococcal infection.

Since all cases of rheumatic fever, even those in which the diagnosis was followed by a question-mark, were included, it was necessary to divide the series into 3 groups according to the firmness of the diagnosis, from the notes in the record sheets of the patients - except those with a diagnosis of chorea minor, which was classified as firm or probable according to the clinician's opinion. All patients satisfying Jones' (modified) criteria were assigned to group A; those with one major and only one or no minor manifestation, to group B; those with no major manifestation but in whom the "clinical picture" was such as to give reason to suspect the condition, to group C. These groups are referred to as the firm group (group A), the probable group (group B), and the possible group

(group C).

II. Rheumatic heart disease

A. Criteria

In order to make it possible to compare Hall's material and the author's the criteria suggested by the New York Heart Association (NYHA) in 1955 were used for the diagnosis of rheumatic heart disease.

The roentgenological findings were evaluated by two independent observers (P.A. and B.P.); and the physical findings by one (B.P.), but in all doubtful cases the findings were re-evaluated by B.W.J. (Chief of the cardiologic unit). The criteria for rheumatic heart disease were thus as follows.

Aortic incompetence

The diagnosis was made on the basis of the characteristic diastolic murmur, which is high-pitched and blowing in character and located in the left or the right third intercostal space. Systolic murmur over the aorta may sometimes occur without being due to aortic stenosis. In advanced cases radiography will often show enlargement of the left ventricle and electrocardiography left ventricular hypertrophy.

Aortic stenosis

Aortic stenosis is usually seen in association with incompetence of the aortic valves. The diagnosis is based mainly on a systolic thrill in the right second intercostal space - though not necessarily - and a low-pitched systolic murmur which is loudest in the right second intercostal space, but which radiates over the entire thorax and up over the carotid arteries. Roentgen examination will often reveal an enlargement of the left ventricle and sometimes calcification at the site of the aortic valves, and electrocardiography left ventricular hypertrophy.

Mitral incompetence

Mitral incompetence is characterized by a pan-systolic murmur, best heard in the apical area and usually transmitted to the left axilla. Roentgen examination will often reveal enlargement of left ventricle and atrium, and electrocardiography often left ventricular hypertrophy.

Mitral stenosis

The characteristic findings are a loud, snapping first sound and a split second with a low-pitched presystolic and/or early diastolic murmur, often throughout diastole. The second sound over the pulmonary area is often accentuated. Roentgen examination usually shows an enlargement of the left atrium and, in advanced

cases, of the right ventricle and a dilatation of the pulmonary artery. Electrocardiography may show a right ventricular hypertrophy and large, notched P waves.

Tricuspid and pulmonary lesions

Tricuspid and pulmonary valvular lesions were diagnosed only in a few cases and then always on the basis of auscultation, roentgenography and phonocardiogram.

1. Comments

The criteria suggested by the NYHA in 1955 are also satisfied by other valvular deformities such as syphilitic, arteriosclerotic and bacterial deformities and it is not always possible to distinguish them from rheumatic heart disease by clinical examination, except the syphilitic cases, which were excluded. Rheumatic heart disease (RHD) or VOC is to be understood as chronic valvular heart disease, of so-called rheumatic type; while the acute form of RHD is dealt with in the chapters on rheumatic fever, and will be referred to as acute endo-myocarditis or peri-carditis.

CHAPTER V

RHEUMATIC FEVER

I. Frequency

A. Variation of frequency of rheumatic fever with the population of Malmö during the study periods

The total number of cases of rheumatic fever in 1930-70 was studied (Fig. 1) for any variation with the population during the years in question. A substantial increase was found for 1940-50, i.e. during and immediately after the end of the war when food was still rationed and socio-economic factors unfavourable. But apart from these few years the frequency of rheumatic fever was declining.

For the sake of completion, the annual number of cases was studied also for the 1970-79 period (Fig. 1). During the period the frequency fell markedly from 2.6 cases per 10 000 inhabitants in 1930-34 to 0.2 in 1970-74.

The cases at Rönneholm children's hospital are included in the frequency table, but were not in the following analysis because they were not part of Hall's material and would have impaired comparisons. The actual number of cases per 10 000 inhabitants for 5 years is given in Table I.

B. Frequency of criterial symptoms and signs

The total material included 729 cases of firm rheumatic fever, 91 probable and 325 suspected cases i.e. all together 1 145 (Fig. 4). The frequencies of the various symptoms and signs given by Jones' criteria for the condition vary from one part of the world to another. In our material the symptoms and signs most commonly met were polyarthrititis, raised ESR and signs of previous streptococcal infection, which were noted in respectively 798, 702 and 663 cases. These criteria were found in most cases of rheumatic fever. These frequencies were followed by those of carditis, which was diagnosed in 199 cases, and joint pain, which was noted in 186 cases in addition to those patients who had polyarthrititis. This latter group probably contained some in whom multiple synovitis could not be firmly diagnosed owing to incompleteness of notes in the patients'

YEAR	CASES PER 10 000 INHABITANTS AND YEAR
1930-1934	2.6
1935-1939	2.5
1940-1944	3.3
1945-1949	2.8
1950-1954	1.1
1955-1959	1.0
1960-1964	0.8
1965-1969	0.4
1970-1974	0.2

Table I Table illustrating increase in rheumatic fever during second world war and a fall from 3.3 per 10 000 inhabitants per year to 0.2 in recent years.

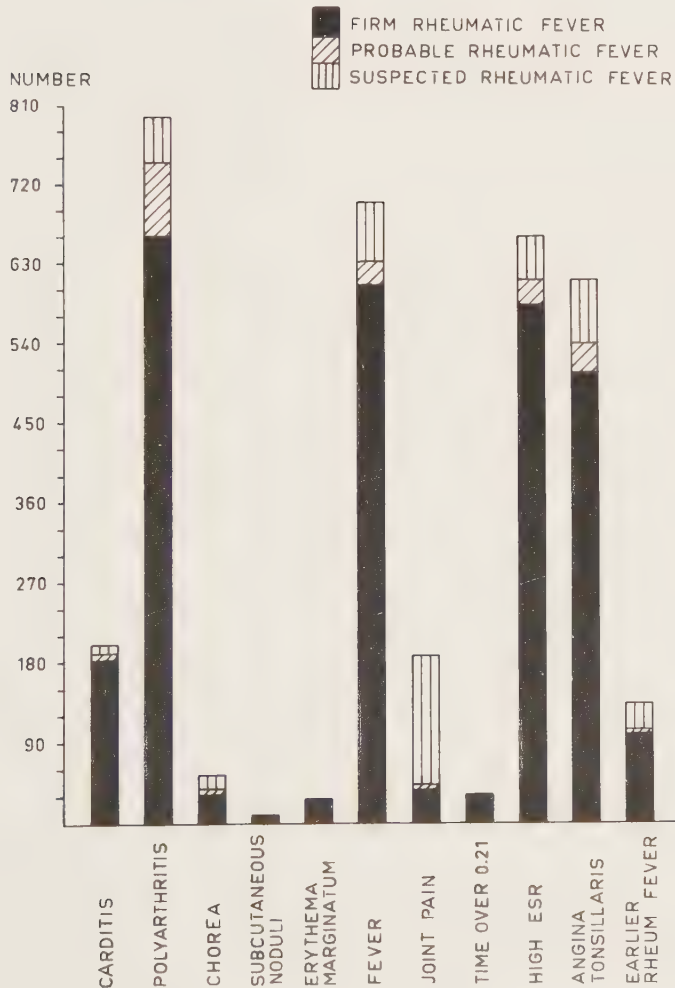


Fig. 4 Distribution of Jones' criteria met in patients with rheumatic fever in their history.

records. Earlier rheumatic fever fulfilling the criteria used was found in 132 cases. Chorea, subcutaneous nodules and erythema marginatum as well as prolonged PR-interval were surprisingly rare. The latter was all the more noteworthy since most of the patients had been examined with ECG during the acute stage of rheumatic fever and these recordings were re-examined at the journal study. In addition to the cases of carditis and chorea associated with rheumatic fever there were other cases of endocarditis and chorea that did not meet the criteria for rheumatic fever and are therefore accounted for separately in the groups of carditis and chorea.

C. Age at onset

The mean age at onset of the rheumatic fever did not vary to any noteworthy extent with the degree of certainty of the diagnosis and was, on the average, 22 years with only little variation (Fig. 5). For endocarditis in rheumatic fever it was about 26 years for the entire group, while in the less certain cases there was a wider range of variation. The mean age at onset of chorea was about 10 years.

D. Age at onset of rheumatic fever and recurrences

Fig. 6 gives the age distribution of patients at onset of rheumatic fever and recurrences. In the present material rheumatic fever was very rare in children below 5 years and was most common between the ages of 5 and 30 years. However, several cases occurred in advanced age. One fifth of the cases were recurrences, but they rarely occurred in children below 10 years.

E. Sex distribution

There was a slight overrepresentation of females, but not so large as that for rheumatic valvular defects (Fig. 7). About three fifths of the material were females. This suggests not only that women have a greater tendency to get rheumatic fever, but also a greater tendency to develop secondary rheumatic valvular lesions.

F. Distribution of primary attacks and recurrences during the study period

The diagram shows the total number of cases of rheumatic fever in 1930-70 (Fig. 8). The total material included also cases with recurrences in patients who had had their first attack of rheumatic fever before 1930. The earliest rheumatic fever that was noted and which is included in the group of valvular defects dates back to 1880-85.

It is remarkable that the number of cases of rheumatic fever during and after

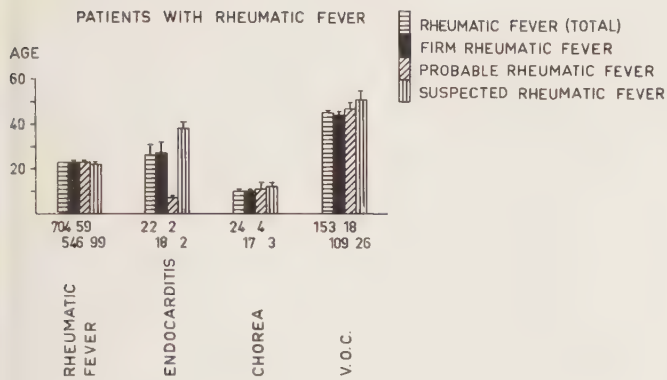


Fig. 5 Distribution of age at onset in patients with rheumatic fever, endocarditis, chorea and VOC in their history.

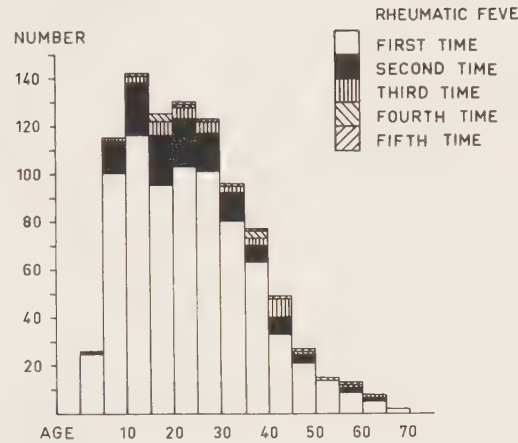


Fig. 6 Age at attacks of rheumatic fever and recurrences.

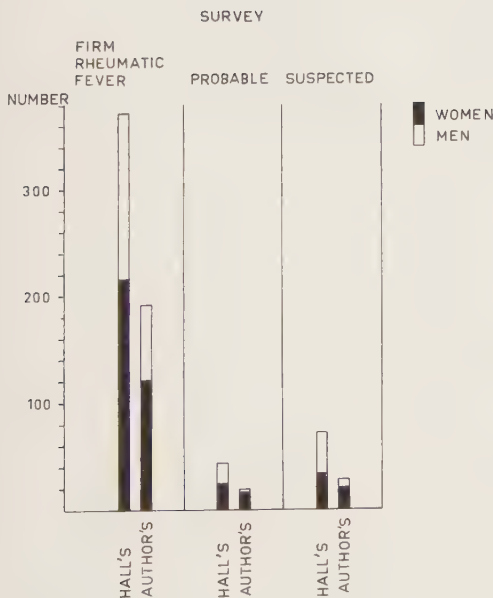


Fig. 7 Sex distribution of patients with history of rheumatic fever.

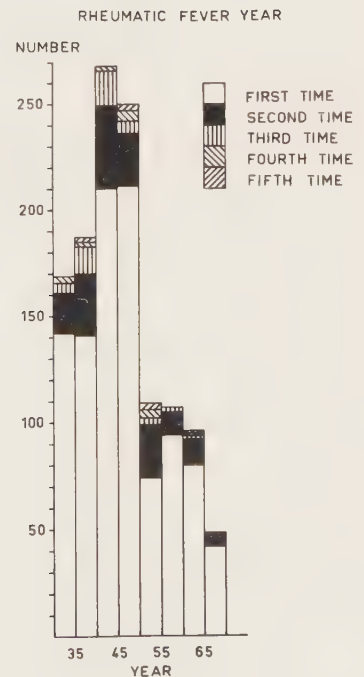


Fig. 8 Recurrences of rheumatic fever.

the war, 1940-50, was about 50 % higher than before that time. This is, however, in agreement with the findings by Olesen and Tybjaerg-Hansen in Denmark.

Penicillin was used in Malmö for the first time in 1944, when it was given to the crews of damaged American bombing aeroplanes which had landed there. Only in exceptional cases could Swedish citizens be treated with penicillin, and even up to 1950 penicillin was still scarce and used only in cases of manifest rheumatic fever, but not in streptococcal tonsillitis. After penicillin had become readily available in Sweden all cases of tonsillitis of suspected streptococcal origin have been treated with penicillin. But no continuous efforts have been made to introduce regular primary or secondary long term penicillin prevention of rheumatic fever. Patients with a history of rheumatic fever have, however, regularly been treated with penicillin if their disease was suspected to be due to streptococci. The frequency of rheumatic fever fell continuously even after 1950 when already the treatment with penicillin must have been very common in tonsillitis. This might be explained by e.g. improved socio-economic and nutritional standard and/or the availability of penicillin for prophylaxis. We have tried to find out the total number of prescriptions given in Sweden. But no governmental or military statistics existed before 1964.

One problem in the estimation of the frequency of rheumatic fever is that occasional patients seen at the children's hospital have had sore throat with co-existing mild joint symptoms but without any involvement of the heart, i.e. patients that did not meet Jones' criteria and in whom no rheumatic fever was diagnosed. Whether these cases, which were, as a rule, treated with penicillin in the acute stage of the acute tonsillitis, really represented abortive rheumatic fever capable of leading to late complications was not possible to decide because we had no possibility to review these patients.

The number of cases of rheumatic fever in 1970-79 was assessed from the archives in the same way as in the years studied in an effort to bring the study up to date. The trend found was unchanged even after 1970 with all together 20 cases until and including 1979.

G. Distribution in the period of the two materials

Fig. 9 shows the frequency of rheumatic fever distributed between primary occurrences and recurrences in Hall's material. These cases were thus diagnosed in 1930-54, but some of the patients had had rheumatic fever also outside this period. The number of cases with rheumatic fever was strikingly high in 1940-50, especially the primary initial attacks. Even during that part of the total period of observation when penicillin was freely available the decline in frequency seemed to be falling more steeply than the reported overall mondial

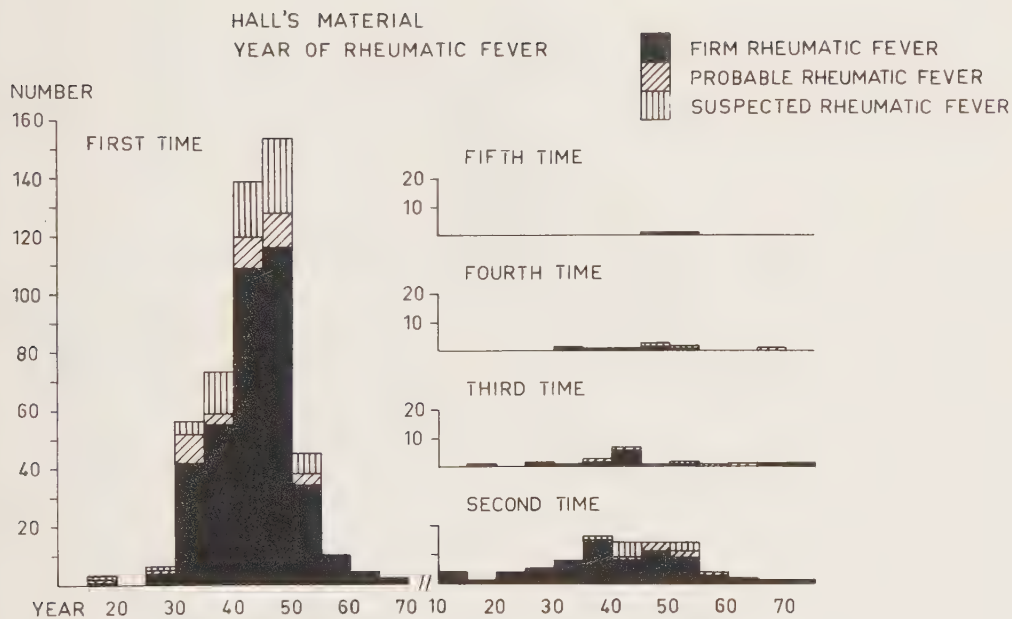


Fig. 9 Recurrences of rheumatic fever in Hall's material

decline. This may perhaps be ascribed to socio-economic factors. It was also shown that the frequency of recurrences was somewhat higher at that time, probably because the study was started in 1930, i.e. before of penicillin. In the author's material (Fig. 10) in which cases of rheumatic fever with and without lesions were not separated the decline was more marked and the frequency of recurrences was low. The causes were probably among those mentioned earlier.

II. Special groups of interest

A. Patients with only carditis, polyarthrititis or chorea without co-existing rheumatic fever

Only a few patients showed evidence of any one of the above conditions without co-existing signs of any other of Jones' criteria for rheumatic fever. There were in all 6 such patients. Of those, 2 with isolated chorea developed rheumatic organic heart disease, while the remaining 4, i.e. those with carditis or and polyarthrititis, did not develop any rheumatic lesion.

B. Nephritis in rheumatic fever

Glomerulonephritis is another important sequela after streptococcal infection and is caused only by certain strains, often from skin infections. It was therefore thought worth while to study the involvement of the kidneys in rheumatic fever. Most of the records gave the results of examination urinary sediment, and notes about the occurrence of nephritis with granular cylinders in the urinary sediment were routinely interpreted as clear signs of nephritis, pronounced hematuria as a probable sign and the diagnosis of nephritis or suspected nephritis without these findings, as possible nephritis. The interpretation was, of course, not firm since a streptococcal origin was not always demonstrable with certainty. It is clear from Fig. 11 that renal involvement of any of these degrees as judged by the above criteria, is not uncommon in association with rheumatic fever. The tendency is somewhat stronger if the diagnosis of rheumatic fever is firm. Almost all those with signs of renal involvement belonged to the group that did not develop rheumatic lesions of the heart, which suggests that nephritogenic streptococci rarely involve the endocardium but can probably produce a clinical picture resembling that of rheumatic fever.

C. Scarlatina

Since scarlatina (scarlet fever) is caused by streptococci it is of special interest in the etiology of heart lesions. When designing the present investigation we considered the possibility of reviewing all the 2 000-3 000 patients who had been admitted to hospital with scarlatina. It was, however, concluded that it

AUTHOR'S MATERIAL YEAR OF RHEUMATIC FEVER

63

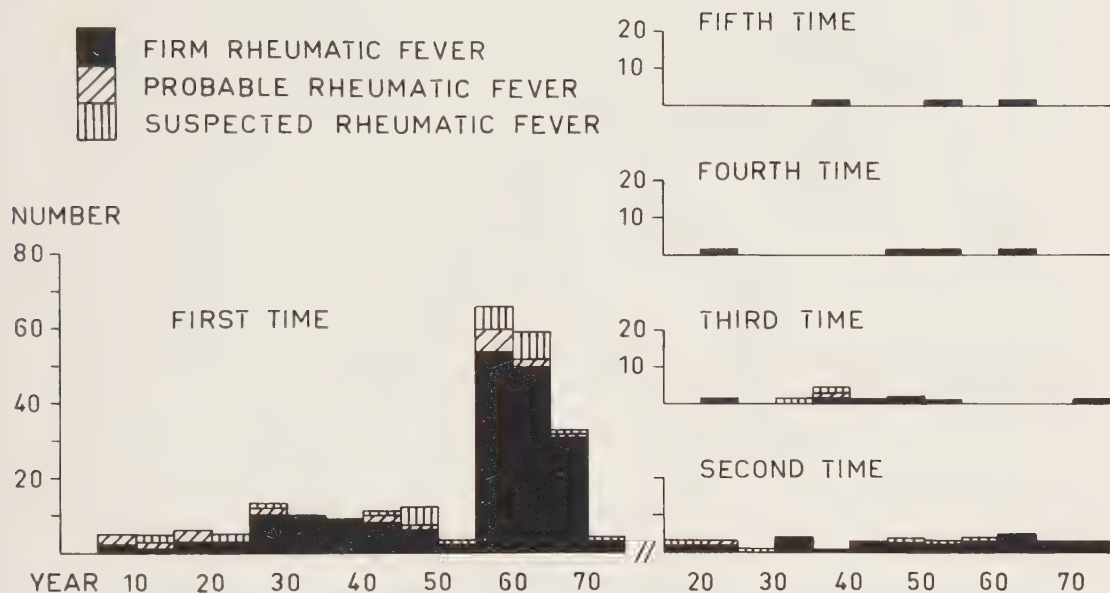


Fig. 10 Recurrences of rheumatic fever in author's material.

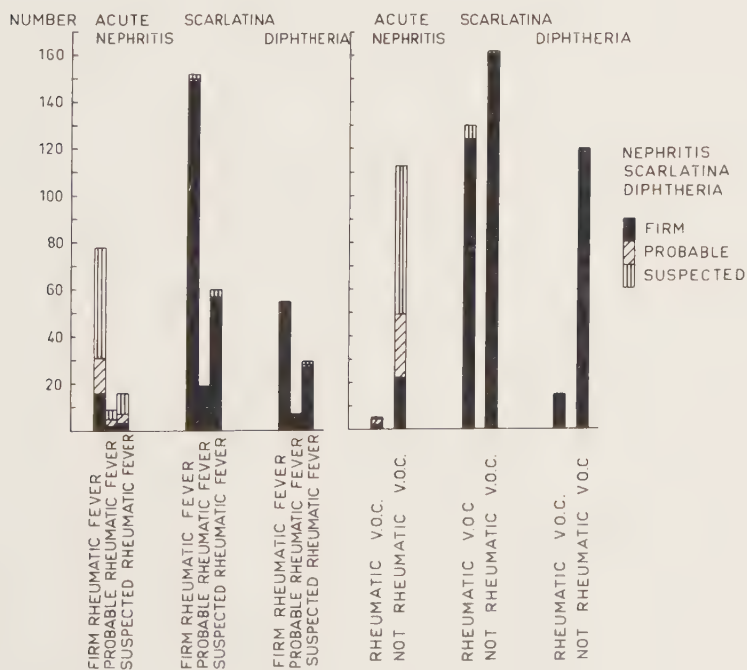


Fig. 11 Diphtheria, nephritis and scarlatina with varying degree of firmness in patients with rheumatic fever in their history and with rheumatic heart disease.

would be difficult to evaluate the findings from an epidemiological point of view because once the streptococcal origin of the disease had been established, many of the patients were cared for at home. The cases diagnosed by practitioners had not been registered. The cases diagnosed in hospital represent serious cases with complications and do not represent the total picture. It was therefore not considered worth while to carry out such a comprehensive review of a material selected from the very beginning.

All the patients in the study were asked whether they had had scarlatina (Fig. 11 and 12). Many had, and this suggested a certain overrepresentation of scarlatina in a rheumatic material, which was not unexpected since streptococci play a role in both scarlatina and rheumatic fever. The frequency of scarlatina agreed fairly well with that of rheumatic fever. The total number of scarlatina cases is, however, much higher.

D. Diphtheria

Carditis is a common complication of diphtheria of classical type. The patients given in Fig. 12 were included in the study because they had had rheumatic fever and not because they had had diphtheria. Fig. 11 shows that the distribution of diphtheria was largely the same in the whole group of patients with rheumatic fever, a distribution which seems reasonable because the disease was not uncommon up to the introduction of vaccination after the second world war. Among the patients who developed a rheumatic defect the frequency of diphtheria was remarkably small, which weighs against the development of lesions of the type regarded as being of rheumatic origin.

E. Diphtheria and scarlatina in Sweden from 1918

The frequency of scarlatina during the study period was about 10 000 per year. A few peaks were, however, found in 1937-51 and in 1959. From the beginning of the 1960s the figure was 6 000 or somewhat lower, which might be explained by the changes in the rules for registration of scarlatina.

The frequency of diphtheria in Sweden was highest the first few years after the first world war (Fig. 13) and, though less so, also after the second world war. From the beginning of 1950 only few cases of diphtheria have been reported in Sweden. The situation in Malmö was similar and has been described in Johansson's (161) thesis on complete heart block.

F. Erythema nodosum

Erythema nodosum is an allergic reaction to, for example, streptococci, tuberculosis, *Yersinia enterocolitica*, sarcoidosis and sulpha therapy. We therefore

NUMBER

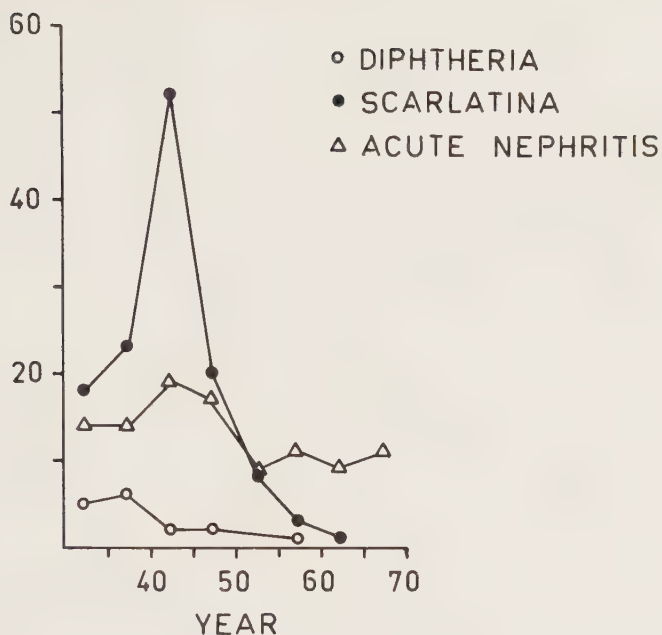


Fig. 12 Distribution of diphtheria, scarlatina and acute nephritis. Absolute number of patients with scarlatina or diphtheria is decreasing, but owing to increase in population the relative number of cases of acute nephritis is fairly steady.

NUMBER

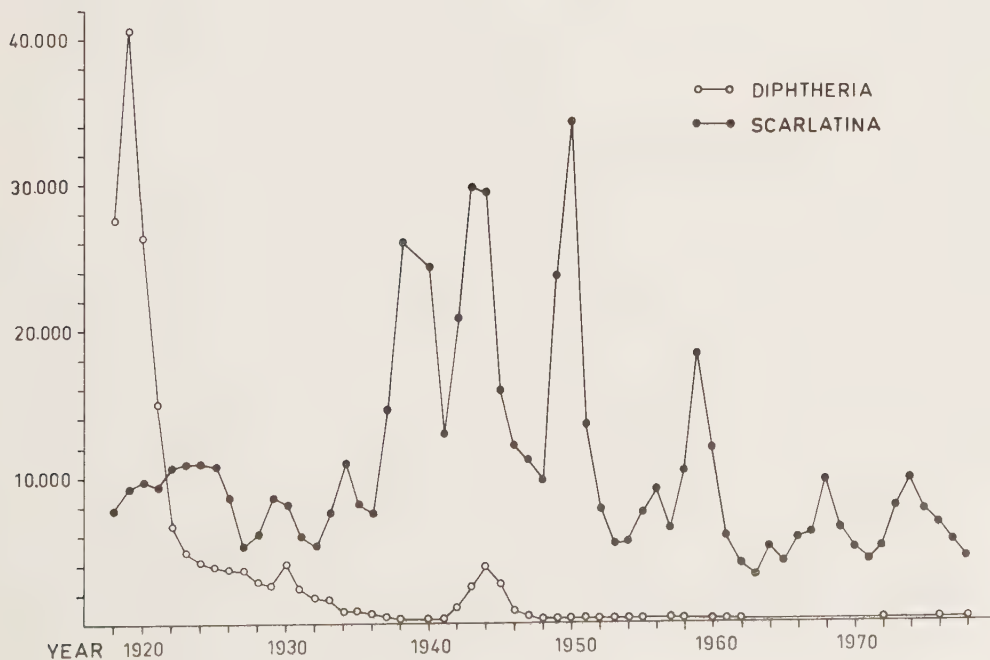


Fig. 13 Frequency of diphtheria and scarlatina in Sweden.

studied the frequency of erythema nodosum in association with rheumatic fever. Erythema nodosum was considered to have occurred when a clear diagnosis had been made in hospital or when the patient had given a clear description of it. Our material contained no evidence of any cause other than streptococci, though other cases could not always be excluded. The occurrence of erythema nodosum seems to be commonest in the somewhat higher age classes and highest in the 25-35 year class. Since all together 91 patients in the rheumatic fever group had had erythema nodosum, it cannot be regarded as a negligible symptom in rheumatic fever, although this is seldom reported.

G. Ornithosis and rheumatic fever

All the patients with VOC were asked whether they had or had had any cage birds and whether they had had ornithosis. Only one answered in the affirmative and that patient had rheumatic VOC. A single case cannot warrant any conclusions. Of the group of 102 patients that had had rheumatic fever and developed a rheumatic lesion, 49 had or had had cage birds.

Of the group that developed rheumatic lesion without having had rheumatic fever the corresponding figures were similar, namely 22 of 46. Thus, our figures provide no evidence that ornithosis is of any significance in the causation of VOC since more than half of our previously mentioned age-matched reference material had had cage birds.

Our figures argue so strongly against any connection between ornithosis and rheumatic defects that a more extensive investigation did not seem warranted, even if it would have been possible in the Malmö material. It would appear that ornithosis need no longer be regarded as a cause of rheumatic heart lesion.

III. Relation between rheumatic fever, carditis and chorea

A. Age at onset

The age at onset of rheumatic fever, carditis and chorea is given in Fig. 14. The table comprises the primary attacks of the disease, but not recurrences. The age at onset of rheumatic fever in our material with a relatively high hygienic standard and relatively good socio-economic standard is higher than that in other series on record. The incidence of rheumatic fever is concentrated to the ages of 5-30 years, but there were a few cases of classic rheumatic fever even in the higher age classes, the oldest patient being over 70 years.

For technical reasons, also the totals of the cases of carditis are given. They were substantially fewer and concentrated mainly in the 5-20 year age class.

As for chorea, it was most common in patients below 25 years with a median of about 10 years.

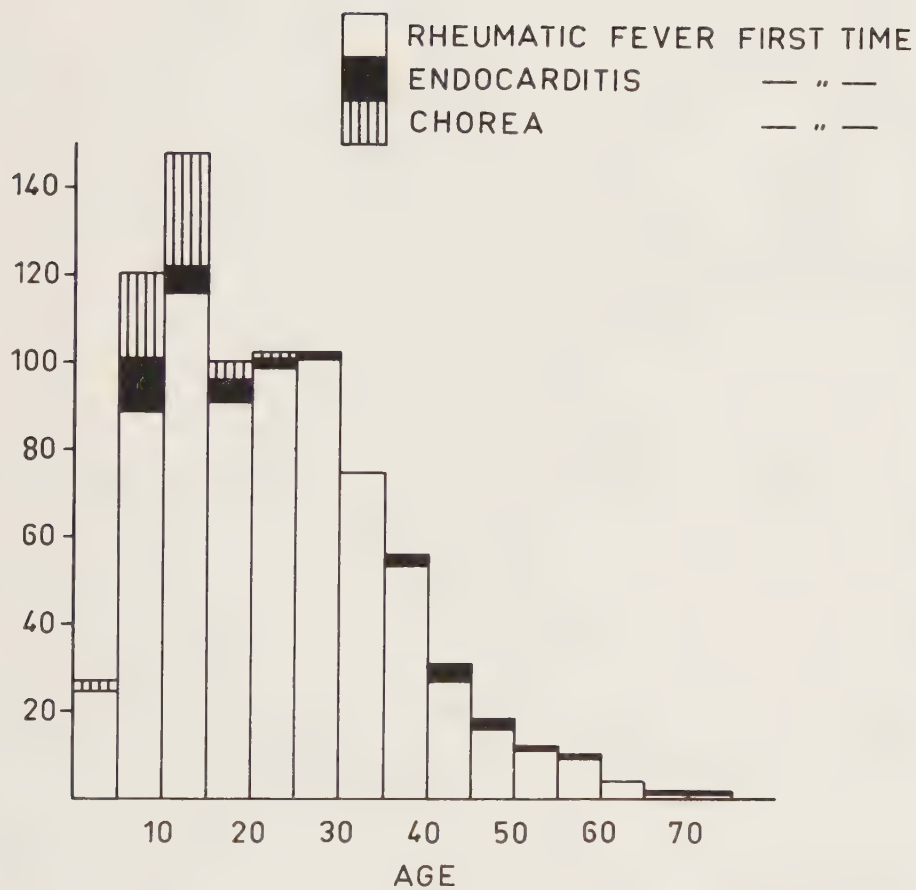


Fig. 14 Age distribution of first attack of rheumatic fever.

B. Chorea

It is remarkable that of the 95 patients with chorea, only 54 had had rheumatic fever really meeting the criteria. Polyarthrititis had been noted in 34 patients, fever in 30 and angina tonsillaris in 22. The raised ESR in 24 was not a common complication of chorea. Joint pain and prolonged PR-interval were rare. Thus, other signs of rheumatic fever were not predominant in the picture of chorea.

C. Carditis

All together 220 patients had had carditis either alone or combined with rheumatic fever. Rheumatic fever had been diagnosed with certainty in 198 and polyarthrititis in 138. Fever had been diagnosed in 160, increased ESR in 155 and earlier sore throat in 132. Only 18 patients had a prolonged PR-interval. Chorea, subcutaneous nodules, erythema marginatum and earlier rheumatic fever filling the previously mentioned criteria were rare in the carditis group. This was rather remarkable since, according to the literature, carditis is more common in association with recurrences.

D. Cases of isolated chorea or carditis

The number of patients who had chorea but not rheumatic fever was small, namely 23, but the average age at diagnosis was higher, however. Only one of them was below 15 years.

All uncertain cases of carditis were excluded. Most of the 15 patients with isolated carditis had had the condition before 20 years of age, but 3 were 35-55 years at onset.

As for the frequency of chorea and carditis at Rönneholm children's hospital, which was not included in Hall's investigation, there were a further 9 cases of carditis in 1930-50. In 1950 that hospital was closed.

IV. History and physical findings

A. Anamnestic data in rheumatic fever

Inquiry was made into the histories of 824 patients. Valvular defects in the parents were noted in 54 and in siblings of 38, which means slightly higher figures than for the Swedish population as a whole. This might be explained, at least partly, by factors other than heredity, such as dwelling environment. Seventy-eight of the 824 patients had also other relatives with rheumatic fever. Also this figure was not unexpectedly higher than the average for the period in question.

Forty-three patients reported that they had had rheumatoid arthritis, a figure over the upper limit of the presumably normal range for the Swedish population as a whole.

Erythema nodosum was noted in as many as 88 of the patients, which means a clear overrepresentation, and corroborates that the condition is a common sign of streptococcal infection and perhaps suggests that this group is less resistant to streptococcal infection. The cause of the erythema nodosum was not tuberculosis or sarcoidosis, but sulpha therapy and Yersinia were not excluded with certainty.

One hundred and eighty-two patients had had angina tonsillaris at least 5 times. Though no adequate reference material is available, the above figure suggests an overrepresentation of streptococcal infections in this group. Two patients had had syphilis, a figure not differing from that in the general population. Prolonged unexplained fever was reported by 65 patients, an observation suggesting decreased resistance to infection.

So-called growing pains, namely nocturnal leg pain, in young individuals without synovitis or other symptoms of rheumatic disease was described by 190 patients. No reliable reference figures are available, but the symptom seems not uncommon in young people, at least in our country. The corresponding figure for patients with rheumatic valvular disease was 7, suggesting that growing pains are not of any noteworthy importance in the development of valvular disease.

Angina pectoris was reported by 68 patients, which is probably fairly representative of this age class of the general population.

Myocardial infarction was reported by all together 16 patients.

Two hundred and nineteen patients had been admitted to hospital because of some form of heart disease.

Fifty-six patients had been examined with catheterization of the heart and 39 had undergone heart surgery, figures reflecting the incidence of rheumatic valvular disease in the material.

Six hundred and sixty-seven patients complained of shortness of breath, which seems a relatively high figure. Even if some of them had developed an organic heart defect or cardiosclerosis, the figure still seems relatively high. But since these symptoms were subjective their reliability is, of course, debatable. Swelling of the lower legs was relatively uncommon and was reported by only 134 patients.

Ninety-seven patients reported irregularity of the heart rhythm and 31 had submitted to defibrillation. Anemia had occurred in 50.

Difficulty in coping with full-time or half-day employment or household work was reported by a large part of the group, namely 444 patients, including 49 who could not cope with household work. The number with decreased occupational capacity was, however, so large, 395 patients, that it deserves attention in the evaluation of the prognosis of rheumatic fever.

One hundred and nine patients had been granted a sick-pension, a relatively large number due mainly to the development of valvular complications, and arguing

in the same direction as the figures for difficulty in coping with occupational work.

Cerebrovascular lesions had occurred in 26 patients. The average frequency in all inhabitants in Malmö is 6 cases per 10 000 inhabitants per year. Endocarditis lenta, only 11 cases, was uncommon, as were dizziness (128 cases), fainting (15 cases) and accidents (92 cases).

One hundred and sixteen were taking digitalis and 128 diuretics, while only 22 were using antiarrhythmic drugs and 27 nitroglycerine.

Only 29 patients were taking dicoumarol or warfarin tablets and only 6 had a pacemaker.

One hundred and eight patients had hypertension.

As many as 462 patients were under continual medical observation, which suggests that after having had rheumatic fever such patients mean a considerable burden on the national health service.

B. Height, weight and blood pressure

The average height of the men was 173 cm. Although this was 4 cm more than for those who had not had rheumatic fever, and although the difference was significant it did not seem important. The average height of the women was the same for both groups, namely 162 cm.

The average weight of the men with a history of rheumatic fever at the time of the review was 74 kg and did not differ from that of the group that had not had rheumatic fever. The corresponding figures for the women were 64 and 60 kg, i.e. a difference of 4 kg.

In the men the average blood pressure was 150/84 and did not differ from that in those who had not had rheumatic fever, while, in the women the corresponding figures were 154/84 and 157/89, showing a small difference which was significant for the diastolic value.

V. Immunological tests

A. Antistreptolysin titre

All the patients were examined in respect of the antistreptolysin titre, Waaler-Rose test and acryl fixation test to find out whether this group of patients with a history of rheumatic fever and rheumatic lesions showed an increased tendency of streptococcal infections or rheumatoid arthritis.

However, the antistreptolysin titre returned to normal soon after a streptococcal infection. Values regarded as clearly increased and arguing for streptococcal infection, namely above 250, were noted in 73 patients and values above 500 suggesting a recent infection with streptococci were found in 33 patients.

This was somewhat higher than the frequency in blood donors in Malmö given in

the survey of the literature. Patients who have had rheumatic fever might have an increased tendency to streptococcal infections.

B. Rheumatoid factor

In 756 patients the Waaler-Rose (agglutination of sensitized sheep cells) test was negative and 16 had a borderline value. Thirty-three clearly had a positive test, some with a very high titre. These values were somewhat higher than in Malmö's blood donor reference material. Of all together 106 age-matched reference persons, the test was positive in only 2 patients and in one the test had a borderline value.

Since efforts were made not to include first attacks of rheumatoid arthritis in the material and to accept only patients who had had rheumatic fever, the figures may suggest a slightly increased tendency to reaction with antigammaglobulin in the material.

Seven hundred and twenty-two patients had normal values in the acryl fixation test, while in 83 the values were increased and regarded as positive in 62 of them. This means that the acryl fixation test was positive in 9.7 %, which is twice the frequency in the normal population. Of the controls, the test was positive in only 2. Also this method, then, showed an increased frequency of antigammaglobulin.

VI. Rheumatoid arthritis and Bechterew's disease in rheumatic fever and rheumatic valvular disease

Patients who reported known or suspected rheumatoid arthritis were examined more thoroughly. They were questioned in accordance with the diagnostic criteria of the American Rheumatism Association (7, 8). When the findings were positive, roentgenograms were obtained of the hands. Only when both the findings at the interview gave a "definite" diagnosis and the roentgenograms of the hands were positive, was a diagnosis of rheumatoid arthritis regarded as definite.

As for the patients with a history of rheumatic fever, 2.9 % were found to have definite rheumatoid arthritis, which is more than that reported by Linos et al. and also more than the prevalences reported by Hellgren and by Allander for the general Swedish population. There was also a certain tendency to positive rheumatoid factor. These figures may indicate a slight connection between rheumatic fever and rheumatoid arthritis.

Rheumatoid arthritis was noted in 1.8 % of the patients with lesions of the mitral valve, but in none with involvement of the aortic valve. These figures did not indicate any safe overrepresentation of rheumatoid arthritis.

Of the material with rheumatic fever Bechterew's disease was present in

0.3 % which is roughly the same as that assumed for the general population of Malmö and this disease was therefore apparently not overrepresented among the patients with rheumatic fever.

Bechterew's disease was never noted in the patients with valvular disease because patients in whom the lesions were due to Bechterew's disease were not included in the VOC material, and no patient with both rheumatic fever and MB Bechterew developed VOC.

VII. Rheumatic fever - socio-economic considerations

A. Geographical considerations

1. Socio-economic distribution in Malmö in relation to the frequency of rheumatic fever

The patients were distributed among the various socio-economic groups according to Swedner's method (313), which is the one generally used in Sweden. According to this method, members of the learned professions, executives and qualified people working on their own account are assigned to social group I; white collar workers and skilled workers to group II; and unskilled workers, to group III. Families are classified according to the highest social group to which any of its members belongs. Only a few patients refused to report their social group.

In 1955 Werner (358) published her thesis "Malmö och dess tillgreppsbrottslighet" with a social material covering a period close to the middle of the present study period. Fig. 15 gives the density of population per hectare. Fig. 16 gives the density for areas with blocks of flats and residential areas as distinguished from industrial areas, administrative areas, parks and the like. Fig. 17 illustrates an analysis of extreme collections of certain social groups and shows that members of social group I were concentrated in the area of Bellevue and the centre of the town, while social group III was most concentrated in the areas of Möllevången, Södra Förstaden, Östra Förstaden, Kirseberg and certain areas in the south of the town.

Fig. 18 gives the average number of theft criminals in Malmö and shows the highest frequency for areas inhabited by the lower social groups.

2. Rheumatic fever

In the following 4 maps the number of cases of rheumatic fever and lesions in Hall's and the author's material are distributed among respective areas of the town of Malmö at the time of rheumatic fever. The circles in order of increasing size represent 1-2, 3-5, 6-10 and 11-25 patients. Hall's rheumatic fever material, which comprises patients who had had rheumatic fever in 1930-54 (Fig. 19) shows a considerable number in the areas of Möllevången, Östra Förstaden, Kirseberg and Augustenborg. A smaller accumulation was also found in Slottsstaden.

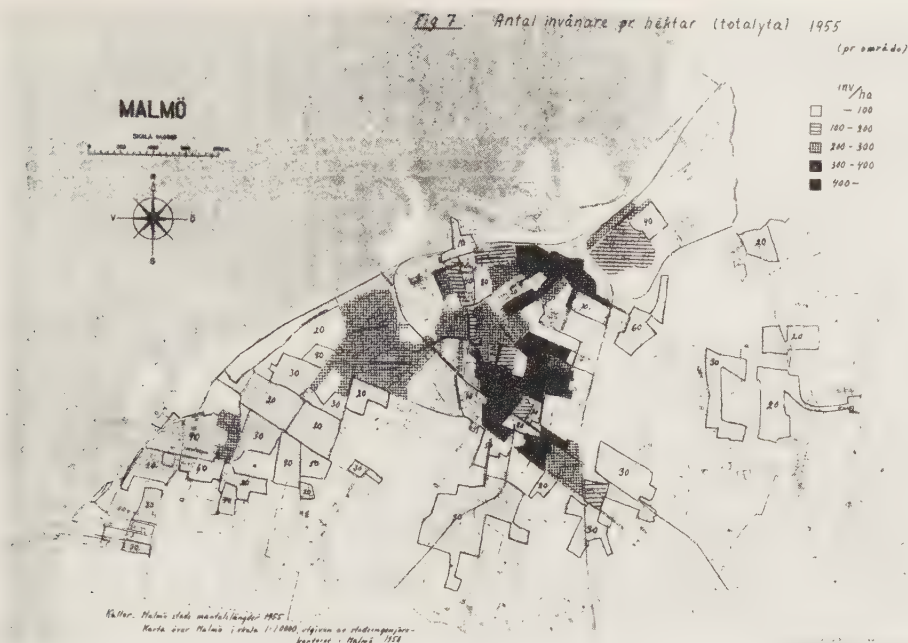


Fig. 15 Inhabitants per 10 000 m² in 1955.

Highest social class predominant in centre and western suburbs;
lowest social class in south and east of centre and suburbs. From
Werner in 1955.

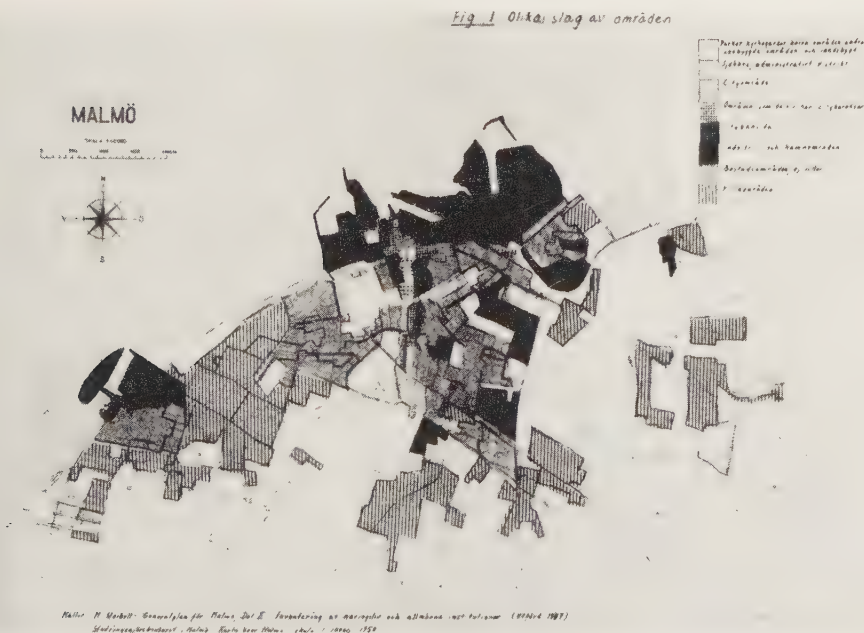


Fig. 16 Type of district. From above:

- 1 Green areas
- 2 Hospitals and offices
- 3 City areas
- 4 Partly city area
- 5 City outskirts
- 6 Industry and harbour
- 7 High houses
- 8 One family houses

From Werner in 1955.

From Werner in 1955.

Fig 17. Områden där minst 50 % av invånarna tillhör samma socialgrupp.



Fig. 17 Areas with more than 50 % of the inhabitants belonging to the same social group. From above 1 I
2 II
3 III

From Werner in 1955.

Fig 18. Genomsnittliga antalet personer pr år vilka registrerats för enkel stöld, inbrott och/eller bil- och motorcykeltillgrepp, anmällda 1951, 1953, 1955, per 1000 mantalshugterna invånare

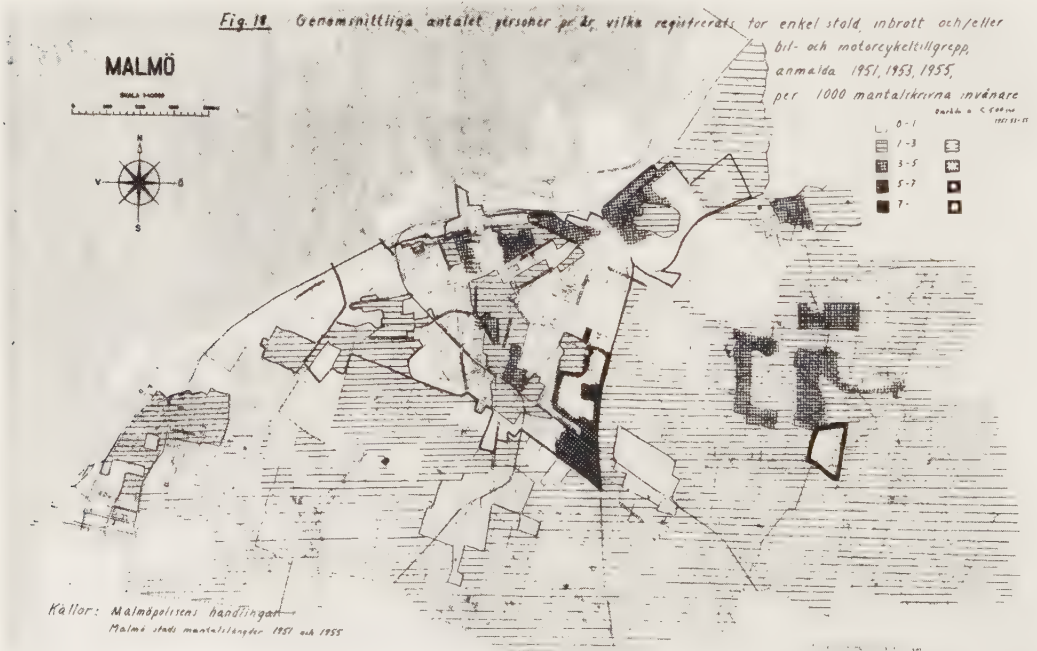


Fig. 18 Places of abode of persons on police register of thieves.

From Werner in 1955.



Fig. 19 Places of abode of patients with onset of rheumatic fever 1930-54. According to size the dots denote 1-2, 3-5, 6-10 and 11-25 patients, respectively.



Fig. 20 Places of abode of patients with onset of rheumatic fever in 1955-70. The dots have denote the same as in Fig. 19.



Fig. 21 Places of abode of Hall's patients with VOC. According to size the dots 1-2, 3-5, 6-10 and 11-25 patients, respectively.



Fig. 22 Places of abode of patients in the present material. The dots denote the same as in Fig. 21.

Otherwise the frequency was low. It is thus obvious that the concentration of rheumatic fever was highest in the area inhabited by social class III. In 1955-70, years covered by the present study (Fig. 20) the distribution of rheumatic fever in Malmö was more even, though still fairly common in the areas of Möllevången and Östra Förstaden.

In the distribution of cardiac lesions after rheumatic fever in 1930-54 (Fig. 21) it should be borne in mind that the rheumatic lesions appear much later, and that the patients had often moved to a new area after the rheumatic fever.

Rheumatic lesions in the present 1955-70 material (Fig. 22) were still somewhat overrepresented in those areas where the rheumatic fever and the lower social groups were predominant, namely Möllevången and Kirseberg, but also to some extent in Slottsstaden and Pildammsstaden.

B. Family income and rheumatic fever

It was thought of interest to study the family incomes. In an endeavour to get as correct an idea as possible we chose the median year 1942, when the population was 187 223, and studied the distribution of incomes from the records of the Tax Authorities to assess the distribution of incomes in different parts of the town (Fig. 23). Their records were not sufficiently exact to be evaluated before 1940. The accumulated income in each of the tax districts is given as triangles and those districts with the lowest average income are placed from left to right at intervals varying with the number of inhabitants. The areas with the highest incomes are thus given to the right. For each such district the accumulated number of patients with a history of some form of rheumatic fever is given as a solid ring. The first 10 districts lowest on the income scale denote rural areas. In these the distribution of the number of cases of rheumatic fever among levels of income was largely normal. Here it is possible that a low income was balanced by larger dwellings and relatively better supply of food from vegetable gardens and domestic animals. Then come the poor districts in the centre of the town, where the curves separate from each other indicating that rheumatic fever is overrepresented in poor districts. In the right part of the curve representing the highest average incomes the curves approach one another indicating that the frequency of rheumatic fever there is low.

C. Distribution of rheumatic fever among social groups

In 1955 8.5 % of the population of Malmö belonged to social group I, 31.6 % to group II and 58.8 % to group III. It is clear from Fig. 24 that the occurrence of rheumatic fever was low in children of parents in group I, but relatively high in groups II and III. The class to which a given individual now belongs is less

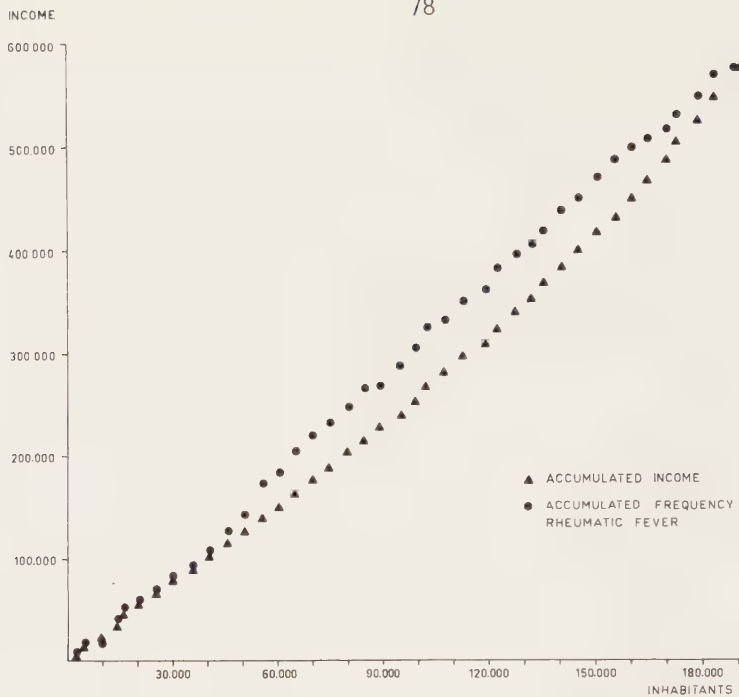


Fig. 23 Variation of accumulated rheumatic fever with accumulated family incomes. The districts are presented from the poorest to the left to the richest to the right. The intervals represent the number of inhabitants in the districts.

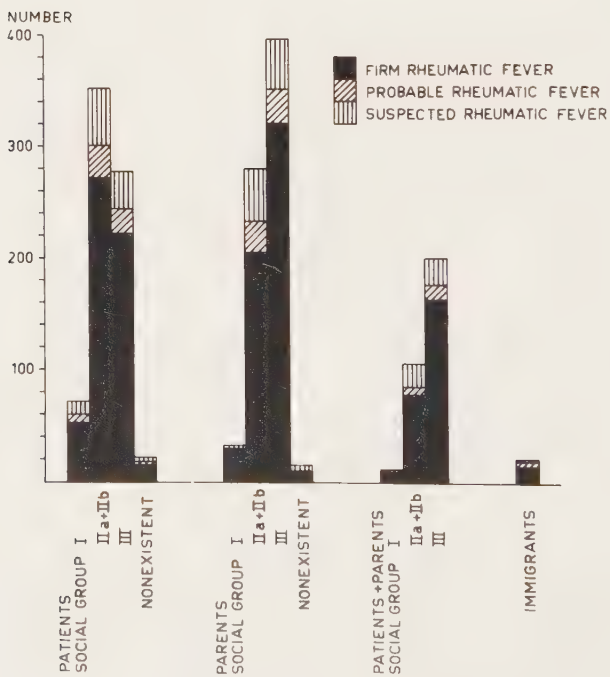


Fig. 24 Distribution of rheumatic fever among social groups.

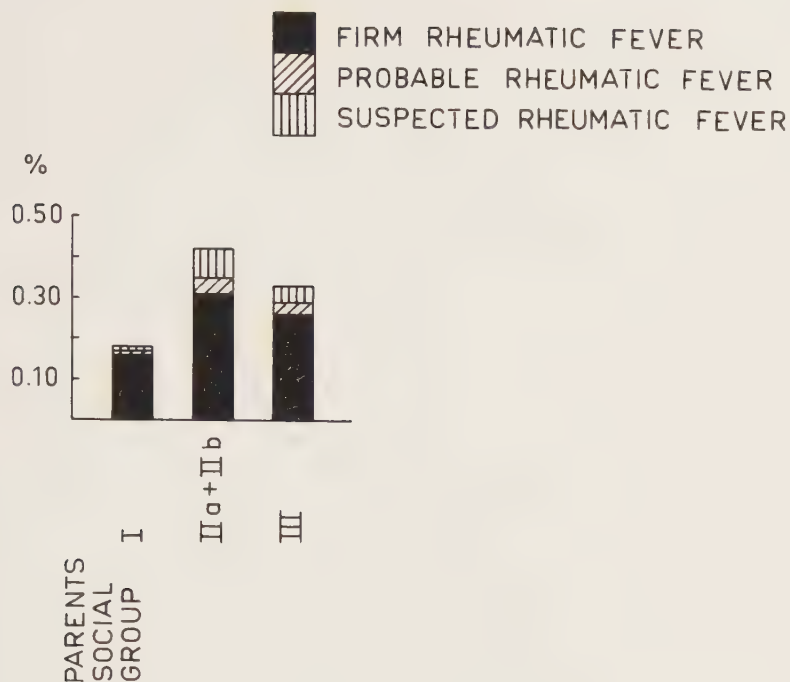


Fig. 25 Percentage of cases of rheumatic fever related to parents' social group. The total population in Malmö chosen as reference.

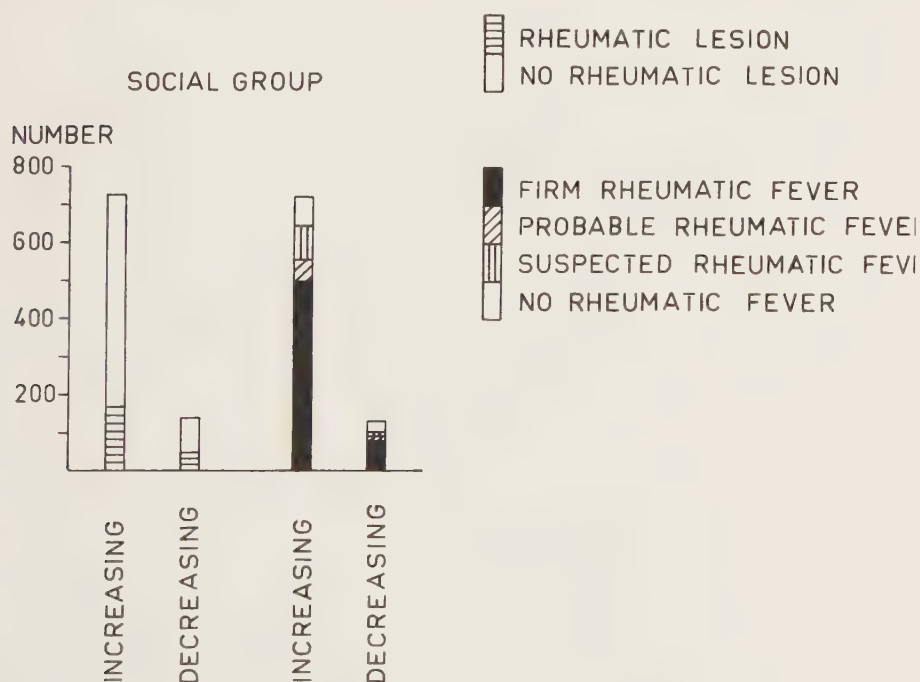


Fig. 26 Histogram showing that the frequency of rheumatic lesions is lower among children belonging to a higher social class than their parents and vice versa.

important since most of the rheumatic fever patients during the time of their certain disease belonged to the same socio-economic class as their parents. A study of those cases in which both parents and the patient belonged to the same social class after he or she had grown up, i.e. cases of "social heritage", it is obvious that social group III strongly dominated (Fig. 24). The percentage of rheumatic fever related to the social group of the parents is; in social group I 0.18, in social group II 0.42, and in social group III 0.33 (Fig. 25). In patients who have fallen in social group (i.e. patients belonging to a lower social group than their parents) the frequency of rheumatic fever tends to be higher (Fig. 26) than in patients belonging to a higher social group than their parents.

The numbers of immigrants were limited before 1960. In November 1960 11 480 inhabitants were born abroad, and 7 005 were not Swedish citizens. For November 1970 the same figures were 23 960 and 18 255, respectively.

Though objections may be raised against the social classification system widely used in Sweden, our figures do show certain differences in the frequency of rheumatic fever with income, residential environment and probably also nutrition.

Judging from all these points of view, it is possible that socio-economic factors play a role in the development of rheumatic fever.

CHAPTER VI

RHEUMATIC FEVER AND RHEUMATIC LESIONS

I. Development of lesions per 5-year period after diagnosis of rheumatic fever
The frequency of rheumatic valvular lesions diagnosed in each quinquennium after the onset of rheumatic fever is given in Table II, which includes some patients in whom the onset of rheumatic fever had occurred before the beginning of the present study period, i.e. before 1930. But the figures referring to the period before 1930 are of less epidemiologic interest because they do not comprise all cases of rheumatic fever at that time, but only those followed by VOC. From 1930 on, the figures for rheumatic fever are correct from an epidemiologic point of view.

By the end of the second quinquennium about 5 % had developed valvular lesions and by the end of the sixth, as many as 10 %. The total number of patients with rheumatic valvular lesions thus tended to increase throughout the study period. The number seems to increase by about 5 % per 15-year period after the onset of rheumatic fever. The frequency of such lesions does not seem to vary with the year of onset of rheumatic fever. This should be borne in mind in the evaluation of the widely accepted belief that rheumatic fever early in life leads to a high frequency of rheumatic heart valvular lesions, for the longer a material is followed up the greater will be the number of patient with such lesions. No true mean interval between rheumatic fever and cardiac lesion can for the same reason be calculated if the material is not followed until autopsy. Higher VOC frequencies are to be found in materials with a long follow-up period.

Table III gives the intervals between the diagnosis of rheumatic fever and rheumatic valvular defects in the 150 dead patients in whom both conditions had been diagnosed. Here, too, the total number of cases of rheumatic valvular defects tended to increase with the interval between the diagnosis of rheumatic fever and the review.

PERCENT WITH VOC

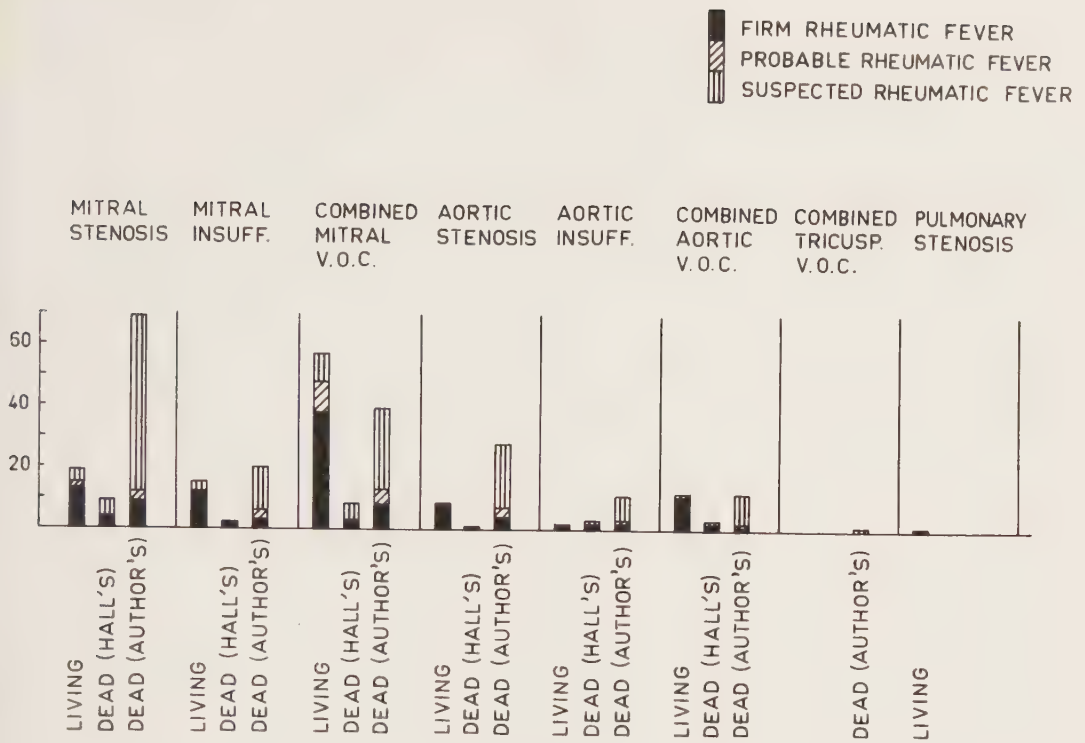


Fig. 27 Distribution of lesions among patients with history of rheumatic fever.

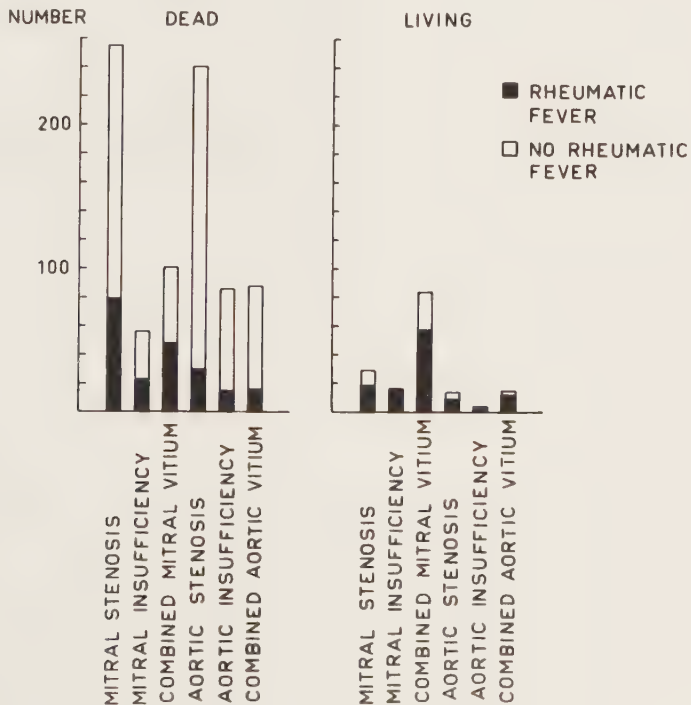


Fig. 28 Distribution of lesions in patients with and without a history of rheumatic fever.

II. Rheumatic fever in the series with VOC

A. Distribution of material among different types of VOC

As expected, among the patients who had died, the frequency of the group with possible diagnosis of rheumatic fever was relatively higher (Fig. 27), possibly because information was available only from their hospital records. Among the patients still alive the frequency of a firm diagnosis of rheumatic fever, irrespective of type of VOC, was higher. This might be explained partly by the possibility to check anamnestically whether the patients had had rheumatic fever. It might, however, also be attributable to the fact that these survivors covered a longer period (1930-70) than the deceased (1955-70), and thereby represented a material in which the patients entered before 1955 had a known rheumatic fever.

B. Relation between year of rheumatic fever and type of VOC

The ratio between the frequency of rheumatic fever and occurrence of cases of VOC was largely uniform throughout the study period. In 357 patients with rheumatic fever in their history the mitral valve had become involved, including 100 with isolated mitral stenosis, and the aortic valve had become involved in 196, including 39 with isolated aortic stenosis.

C. Frequency of rheumatic fever found at review of patients with VOC

Among the survivors reviewed (Fig. 28) there were overrepresentations of combined lesions of the mitral valves and a general dominance of the involvement of the mitral valves. Moreover, the majority of the patients, though by no means all, with VOC had rheumatic fever in their history.

There did not seem to be any correlation between the various types of lesions and frequency of rheumatic fever.

In the group of patients who had died the frequency is lower, especially in those with aortic lesions. This may be due to the fact that studies of the records could not be combined with an interview. In the aortic lesion group the difference is, however, so marked that it may warrant the conclusion that these VOC patients less often had rheumatic fever than those with mitral lesions.

III. Age at onset of VOC in patients with and without rheumatic fever

It was considered of interest to find out whether any difference could be demonstrated between the age at onset of VOC in patients with and without rheumatic fever (Fig. 29). The figures in our material showed that the onset in patients with rheumatic fever occurred most often between the ages of 50 and 75 years, with a maximum between 60 and 65 years. For the patients with a firm diagnosis of rheumatic fever filling Jones' criteria the distribution was somewhat more

V.O.C. AGE IN 5-YEAR PERIODS

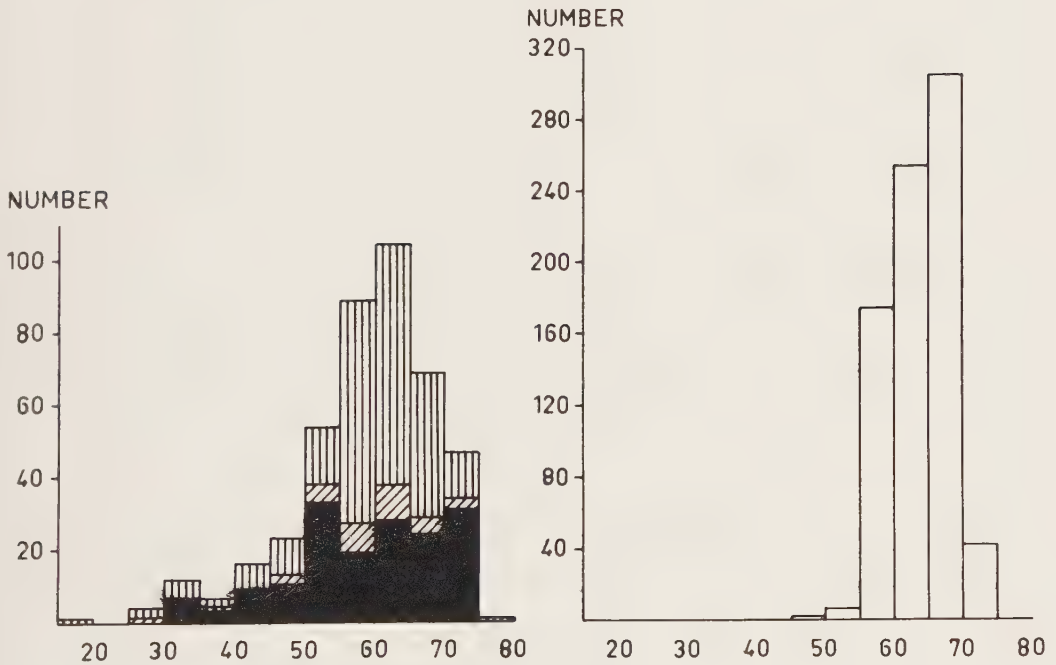
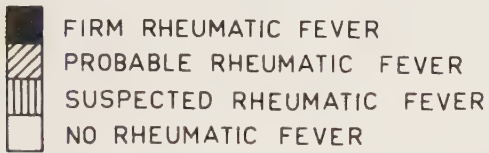


Fig. 29 Age at diagnosis of heart lesions in patients with and without rheumatic fever in their history.

even during the period in question.

In the patients without a history of rheumatic fever the lesions appeared later and were not diagnosed below 45 years of age. In most cases the onset occurred in the 55-70 years of age class with a peak between 65 and 70 years. The frequency curve for these lesions was clearly right-skewed compared with that for patients with a history of rheumatic fever, which suggests that these lesions, which are also regarded as rheumatic, have a natural history different from that of those lesions probably caused by rheumatic fever.

This remarkable finding was thought to warrant further investigation to find out whether these patients without rheumatic fever in their history had any traits distinguishing them from those who had had rheumatic fever, especially since there is evidence that rheumatic fever leads earlier to lesions, particularly of the mitral valve, and the absence of rheumatic fever to a later onset of lesions, particularly of the aortic valve.

IV. Age at onset of rheumatic fever

Dating of the age at onset of rheumatic fever retrospectively in patients with rheumatic valvular lesions is not without problems because of the successive development of new lesions in rheumatic fever with the result that the findings will depend on the age of the patients and thus on the time of follow-up from the rheumatic fever and according to the extent to which the rheumatic fever has led to organic lesions. Of those patients who had had rheumatic fever (Fig. 30), those with combined lesions had had their rheumatic fever at a lower age than those with isolated stenosis or insufficiency. The limits range from those with combined aortic lesions who had had a rheumatic fever at 15 years of age to those with aortic stenosis with rheumatic fever at 30 years. Patients with lesions involving both valves had had their rheumatic fever at a mean age of 20 years. The age at the time of rheumatic fever was, however, highest for aortic stenosis and mitral insufficiency.

As for patients with endocarditis together with rheumatic fever, there were only 4 and therefore warrant no conclusions.

Chorea was rare and seemed to affect mostly the mitral valves. The age at chorea which led to rheumatic valvular defects was, as expected, low.

The age at onset of the actual valvular defect was between 36 and 57 years. The lesions that appeared earliest, namely at 36 years, were the combined aortic lesions and the isolated aortic insufficiencies, while the highest age at onset was 57 years and in isolated aortic stenosis, which suggests that that lesion might also have some other cause. Mitral valvular lesions did not vary widely in age at onset, and for double lesions involving both valves the mean age in the

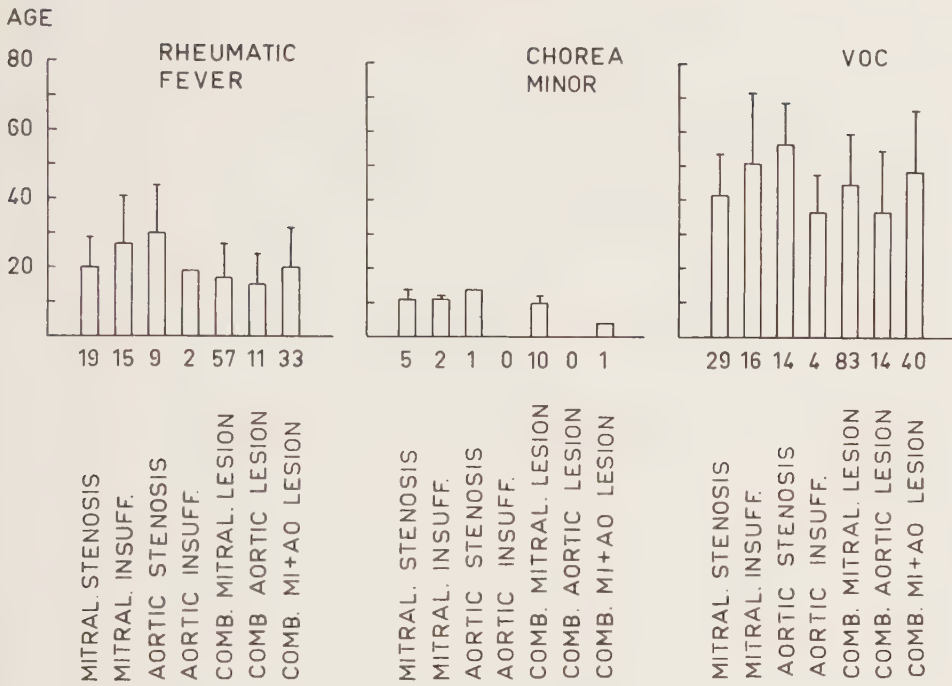


Fig. 30 Age at diagnosis of fever, chorea minor and rheumatic heart disease in patients with various rheumatic heart lesions.

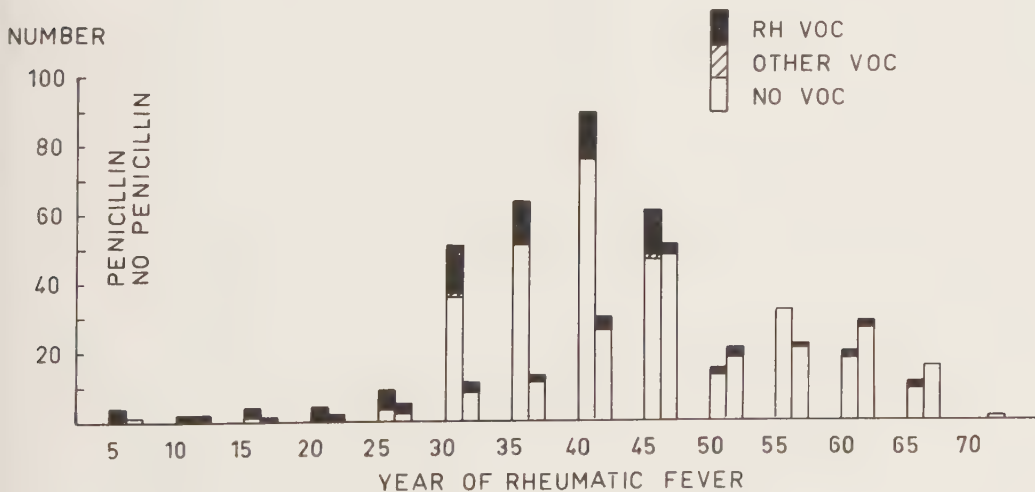


Fig. 31 Frequency, among patients with history of rheumatic heart disease, of angina tonsillaris treated and not treated with penicillin.

group was 49 years.

A. Survey of degree of probability of rheumatic fever

Of the whole material comprising rheumatic fever in 1930-70 and rheumatic lesions in 1950-70, all together 13.5 % of the patients with a firm diagnosis of rheumatic fever developed rheumatic lesions, 3 % of those with probable rheumatic fever and 18.4 % with suspected rheumatic fever. The last-mentioned group included also 2 patients with lesions that could not be regarded as rheumatic but congenital.

V. Penicillin therapy

All the patients were asked whether they had regularly received penicillin for any infections of the throat they might have had.

Unfortunately this question resulted in that patients who had had their rheumatic fever before the advent of penicillin and had since had recurrent tonsillitis obviously tended to answer in the affirmative - although they had little or no chance of having received it before, say, 1947.

Treatment with penicillin proved to be relatively common in angina tonsillaris. The frequency was higher for those who developed a rheumatic lesion than those who did not, namely 73 % and 60 %, respectively. Unfortunately it is not known for us whether the treatment was therapeutic or secondarily prophylactic.

A. Distribution of penicillin treatment according to year of rheumatic fever

The X-axis in Fig. 31 gives the year of the occurrence of rheumatic fever and the Y-axis the number of cases that developed rheumatic lesions. The first and second columns show those cases respectively treated and not treated with penicillin. These columns are given with the same reservation that some of the patients who had had rheumatic fever and probably angina tonsillaris before the advent of penicillin reported that they had always been treated with penicillin for throat infections. The figures are therefore not reliable until after 1950, when penicillin therapy became a routine method.

Generally speaking, penicillin therapy has been common in angina tonsillaris. Yet since 1950 such treatment has been used in barely half of the cases of the condition. It can at any rate be concluded that after 1950 heart lesions were equally common among patients who had and had not been treated with penicillin, though the number of patients with lesions with a history of rheumatic fever has decreased. The table shows no reliable evidence of penicillin therapy per se offering protection against later lesions.

VI. Cortisone therapy in rheumatic fever and its effect on development of heart lesions

All the patients with VOC were asked whether they had been treated with cortisone in association with rheumatic fever. Only 105 answered in the affirmative and 498 in the negative. In contrast with what is described in the literature, we found no striking effect of cortisone on the frequency of late lesions. Of those treated with cortisone, 17 % developed lesions, compared with 23 % of those not so treated suggesting a probable, but not a certain, desirable effect. Since cortisone can thus have some effect there is no reason to stop its use in rheumatic fever. Our investigation could not confirm that the view put forward in international studies that its effect is better when the treatment is started early.

CHAPTER VII

RHEUMATIC LESIONS

I. Patients still alive and reviewed

The material included those of Hall's cases of rheumatic fever in which the lesions were diagnosed in the present study period (1955-70). Even if many of the patients had no history of rheumatic fever, the term rheumatic lesion is used on the basis of the criteria given or autopsy findings.

All together 143 patients had mitral lesions, 72 aortic lesions and 2 had lesions of the right half of the heart and 3 had other types of lesions. In 41 patients the lesions involved both the mitral and aortic valves.

Sixteen of the patients were immigrants. Three of them had mitral stenosis, 8 combined mitral lesions, 2 aortic stenosis and 3 combined aortic lesions. Eight of the 143 patients died during the study period, i.e. between the analysis of the records and the review. It is clear from Fig. 32 that almost two thirds of the present cases had not been included in Hall's rheumatic fever series, but were diagnosed in 1955-70 without a previous diagnosis of rheumatic fever in 1930-44.

II. Types of lesions in relation to rheumatic fever

Fig. 28 shows the frequency of a history of rheumatic fever in patients with various lesions. The frequencies were higher in patients with mitral lesions, especially in those with combined mitral lesions.

III. Frequencies

In Hall's study (1930-54) 200-250 new cases of rheumatic lesions were diagnosed per 5-year period. In the present investigation the frequency was about the same, namely 267 in 1955-60, and about 370 cases in the two following 5-year periods (1960-70). This is remarkable because the frequency of rheumatic fever was declining markedly, especially after 1950. Thus, the absolute number of rheumatic valvular disease had not decreased but, if anything, tended to increase.

Of the patients in whom the lesions were diagnosed in 1955-70, some had, of

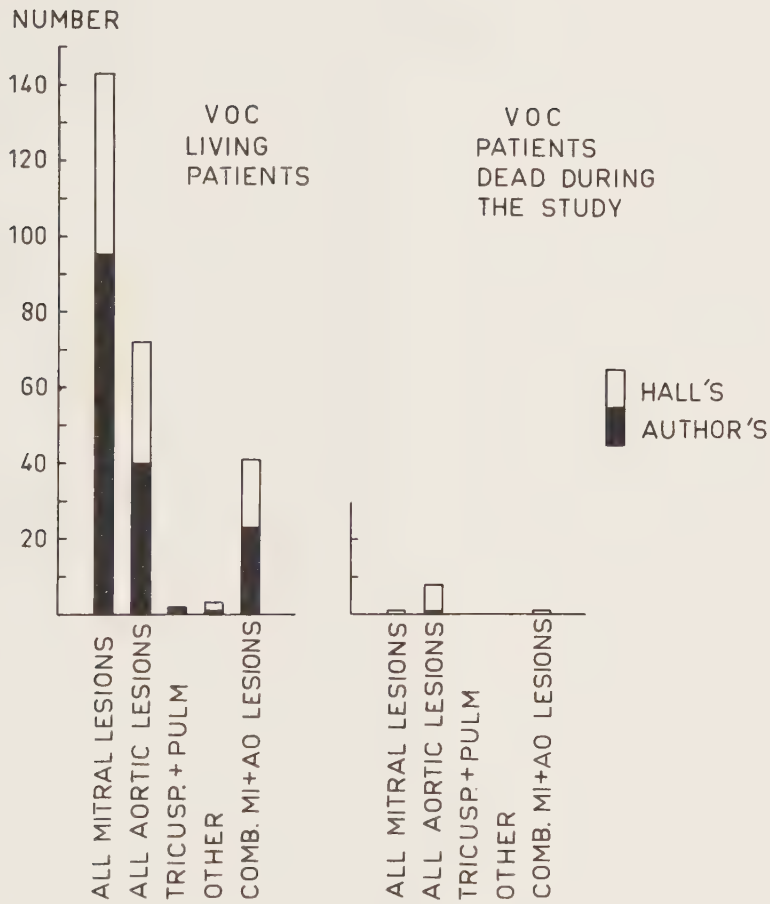


Fig. 32 Distribution of lesions in patients with rheumatic heart disease in author's and Hall's material (only few patients died during the study period).

course, been included in Hall's rheumatic fever series of 1930-54. In the column after 1970 there were some patients in whom lesions diagnosed at the review had probably developed in 1970. That column (after 1970) is thus not really representative. But it is obvious that penicillin therapy and the decreasing frequency of rheumatic fever did not really reduce the frequency of rheumatic lesions in the general population as much as expected. There must be some other factor responsible for this lack of decrease in frequency. The possibilities mostly discussed seem to be that subclinical forms of rheumatic fever might still lead to slowly developing cardiac lesions or viral antigens. The present material offers no definite clues.

A. Rheumatic lesions with and without previous rheumatic fever

As mentioned earlier, the number of cases of rheumatic lesions had not decreased with the decrease of rheumatic fever during the period studied. It is clear from Fig. 33 that the frequency of a previous history of rheumatic fever in patients with lesions successively decreased, while the number of patients with lesions without a history of rheumatic disease increased. This applies in particular to aortic lesions, which are shown in Fig. 29. Also these figures lend support to the hypothesis that not only classical rheumatic fever, for example, but also an abortive form of rheumatic fever not meeting Jones' criteria and not diagnosed, may play a role in the development of the lesions in question. This would imply that the abortive forms do not produce any important joint symptoms, but nevertheless lead to an autoimmune reaction resulting in involvement of the endocardium with progressive fibrosis. The possibility of a cross-antigenicity between the endocardium and virus strains might also provide an explanation. The fact that so many valvular lesions remain concealed until death or post mortem suggests that also the number of slowly developing asymptomatic lesions is, if anything, increasing.

B. Variation of frequency of rheumatic lesions

The number of cases of rheumatic lesions in Malmö in 1930-70 was largely steady. Owing to the growth of the population during that period (Fig. 34) this means that the frequency per 1 000 inhabitants fell by about 40 %. But the frequency of rheumatic fever was, as shown earlier, declining still faster.

Of the patients who had rheumatic fever after 1930 and developed heart lesions, 51 % had died before the review.

C. Time distribution

The total number of patients with rheumatic valvular lesions in Hall's previous work and the present material is given in Fig. 35. The loss of patients during the

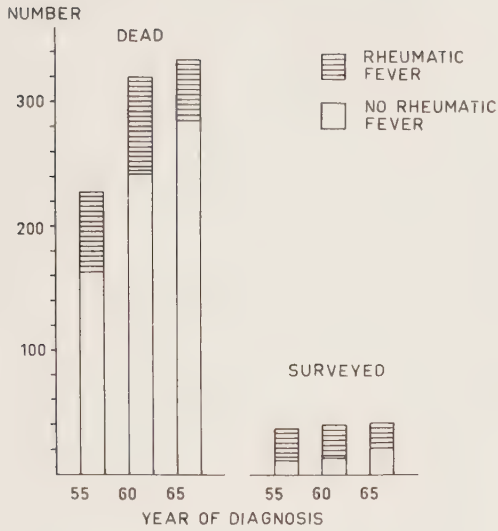


Fig. 33 Patients with rheumatic heart disease with and without history of rheumatic fever.

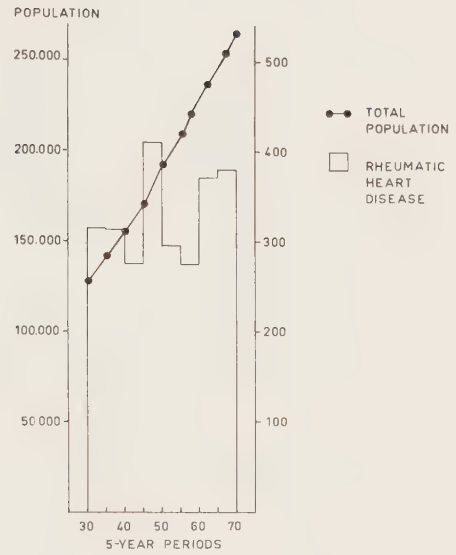


Fig. 34 Total number of patients with rheumatic heart disease in 1930-70 versus number of inhabitants in Malmö. The absolute number of such patients increased, but not so much as the number of inhabitants. The number of cases per 1 000 inhabitants fell by 40 %.

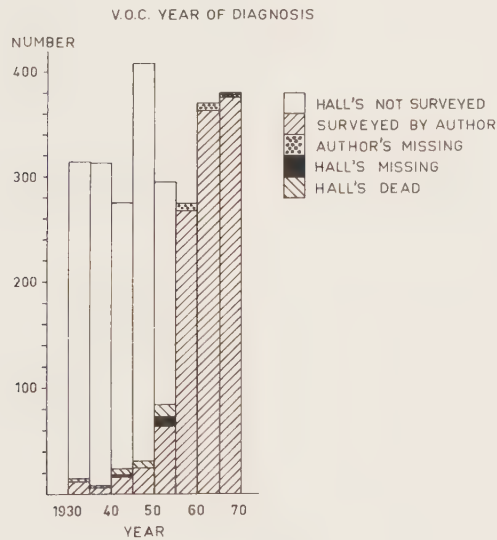


Fig. 35 Rheumatic heart disease 1930-70. Total material. No absolute decrease per 5-year period.

review was only 1.0 %.

The maximal total number of lesions diagnosed fell in the periods 1945-50 and 1960-70. The frequency of lesions showed no tendency to fall during the whole period 1930-70.

The number of patients reviewed in the 1930-54 period belong to Hall's material of patients who had previously had rheumatic fever. The frequency increased with the interval after the rheumatic fever. The lesions diagnosed before 1955 were included in the main evaluation of the lesions. This was done in order to increase the material for evaluation purposes. In tables related to chronological data they will be shown separately. A separate discussion of the course of only the lesions diagnosed 1955-69 will follow separately.

The above mentioned cases diagnosed at the present review in 1974 were referred to the period 1965-70 because the delay of the diagnosis was probably due to lack of symptoms in patients who, as a rule, had had the lesions before 1970.

D. Age at diagnosis of lesions

The age distribution of the diagnosis of the lesions is given in Fig. 36. It should be observed that some of the patients in the acute phase of rheumatic fever had had transient murmurs of varying character suggesting endocarditis according to Jones' criteria. These murmurs were no longer demonstrable at the subsequent controls, and the patients had then had no manifestations of any lesions for a varying period. In those cases where the murmurs in the acute phase of rheumatic fever disappeared the patients were not considered to have had any lesions before the definite onset of clear symptoms of lesions and murmurs. In the patients reviewed the diagnosis of lesions was established with increasing frequency up to the age of 55 years. But new lesions were diagnosed even in very old patients. Rheumatic lesions can appear in early childhood and even up to ages above 90 years.

E. Sex distribution

Of patients with rheumatic lesions, only 30.2 % were men, suggesting that rheumatic valvular defects were much more common in women. This applies in particular to mitral lesions, of which only 24.4 % were diagnosed in men. The corresponding figures for aortic lesions and double lesions were 40.6 % and 37.5 %, respectively.

IV. Earlier natural history and symptoms of defects of the mitral and of the aortic valves

The diagnosis of mitral lesions occurred earlier in life than did the aortic defects, namely 19-20 years and 22-28 years, respectively.

V.O.C. AGE AT DIAGNOSIS

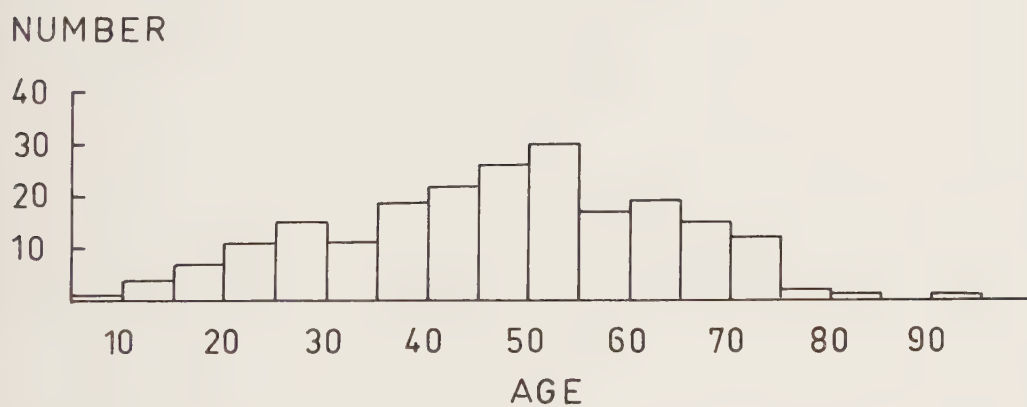


Fig. 36 Age distribution of diagnosis of rheumatic heart disease.

The cases of endocarditis leading to lesions had been diagnosed relatively late in life at, on the average, 44 years except in one case in Hall's material, in which it had been diagnosed in a 12-year-old child, who afterwards developed a defect of the aortic valve.

As for chorea, the onset occurred at the age of about 10-11 years. Twenty-one cases resulted in mitral lesions and one in a lesion of the aortic valve.

Mitral lesions were diagnosed at, on the average, 49 years in the author's material, compared with 38 in Hall's. The corresponding figures for aortic lesions were 50 and 40 years, respectively.

V. Medical history before diagnosis

The patients with VOC were asked the same questions regarding their medical history. Five had parents and 7 had siblings with VOC. Five had a relative with a history of rheumatic fever and 4 had rheumatoid arthritis themselves. One had had erythema nodosum, and 14 had frequently had angina tonsillaris. One had had syphilis and this patient had an aortic defect as well as a mitral lesion which, because of a history of rheumatic fever and the clinical picture, was judged as being of rheumatic origin. Febris incerta causae was reported by 5 patients, growing pains by 7, angina pectoris by 10, myocardial infarction by one. Forty-one had been admitted to hospital for heart conditions and for investigations such as catheterization in 17, for heart surgery in 9 and for heart failure. Hospital care for other serious diseases was reported by 35. Regular check-ups in out-patient care were reported by 185. Shortness of breath was reported by 89 patients, hypostatic oedema by 11, subjective feeling of arrhythmia by 20. Six had undergone cardioversion. Five had a history of anemia and impairment of working capacity had occurred in 55. Cerebral lesions were reported by 5 patients and endocarditis lenta by 3. Five had had severe accidents, 11 fainted sometimes and 2 had attacks of syncope. As for medical treatment, digitalis was taken by 28, diuretics by 24, antiarrhythmic drugs by 5, nitroglycerine by 7 and dicoumarol by 49. Twelve had a sick-pension. Thirty-three had been informed about hypertension. Five had a pacemaker. Eighty-seven had or had had a caged bird, 17 had other contacts with birds and one had had ornithosis.

VI. Findings at review

A. Physical findings

Most of the patients re-examined were under regular medical observation, which might explain the relatively low incidence of symptoms of heart failure. Three hundred and twenty-seven were men and 497 women. Of these, 61 men and 143 women had lesions. The median age of the men was 51.6, and that of the women, 54 years.

Cyanosis was noted in 2 patients with mitral lesions.

Dyspnea was noted in 4 patients with mitral disease and in one with a combined aortic lesion and a lesion of both the mitral and aortic valves.

Oedema was found in 19 patients with mitral disease and in one with an aortic lesion.

Heart enlargement was diagnosed by percussion in 7 patients with mitral lesions and in 4 with aortic lesions.

Rales were heard in 5 patients with mitral lesions, in 4 with aortic lesions and in 3 with double lesions.

Broad upheaving ictus or right chamber pulsations was found in 23 patients with mitral lesions, in 2 with aortic lesions and in 8 with double lesions.

Auscultatory arrhythmia, on the other hand, was relatively common and was noted in 45 % of the patients with mitral lesions and in 19 % of those with aortic lesions.

B. Hypertension

The blood pressure was measured in the right arm with the cuff method using a mercury manometer and after the patients had rested for 10 minutes. The diastolic blood pressure was determined according to phase V. No noteworthy differences were found between the various lesions. The highest systolic blood pressure, 166 mmHg, was found in patients with a double lesion. The highest diastolic pressure, 86 mmHg, was recorded in patients with mitral lesions. The values were 158/86 for pure mitral lesions, 163/79 for pure aortic lesions and 166/81 for bivalvular lesions. For all, the blood pressure was 160/84.

C. ESR

In only 6.2 % of the patients did the erythrocyte sedimentation rate (ESR) exceed 30 mm/hr. The ESR was only slightly raised in the group of patients with lesions. The overall mean was between 13 and 14 mm with a tendency of the levels to be somewhat higher in the patients with mitral lesions. For pure mitral lesions it was 14.1 mm, for pure aortic lesions 13.3 and bivalvular lesions 12.7, respectively. The ESR findings did not suggest any residual activity of rheumatic activity.

D. Haptoglobin

About 4 % of the entire Swedish population have haptoglobin deficiency (235). In the group with lesions, Fig.37, the haptoglobin levels were relatively normal, but lower in patients with aortic lesions and especially in those with double lesions, suggesting somewhat increased hemolysis in the patients with a defective aortic valve.

In the patients with a prosthesis the haptoglobin levels were low. Of the

STANDARD ERROR

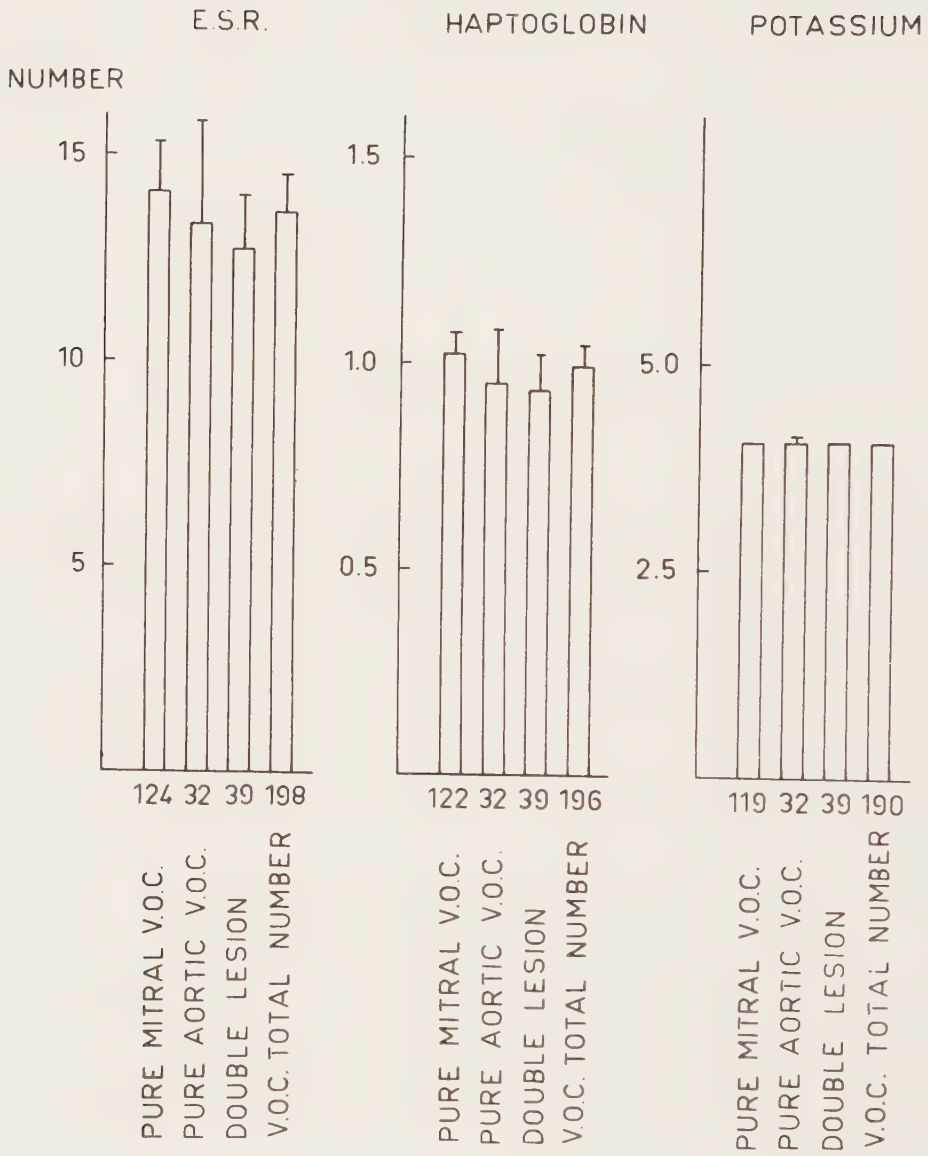


Fig. 37 Laboratory studies.

patients with an aortic prosthesis (7, including 2 with double lesions) four had a value of 0.0, two had 0.3 and one 0.6 and of the patients with a mitral prosthesis, two had 0.0 and one had 0.05. Thus, our patients with prosthetic valves showed definite signs of increased hemolysis.

E. Diuretics and potassium in the entire material of rheumatic fever and rheumatic lesions

One hundred and sixty-seven patients were on diuretics. Most of them were in the 45-60 year age group with only three in the 20-25 year group.

The blood samples were obtained without the use of a tourniquet and without clenching of the hand. The average value of potassium in the entire material was $4.05 \text{ mM/l} \pm 0.03 \text{ SE}$.

The normal range for the hospital laboratory was 3.5-4.5. Of the patients treated with diuretics, 13.2 %, showed a potassium concentration below 3.5 mM/l as against 1.3 % in the patients without diuretic therapy. Corresponding figures for values above 4.5 were 7.5 % and 8.6 %, respectively.

F. Plasma digoxin level in the entire material

Digitalis was, as a rule, prescribed for enlargement of the heart, signs of heart decompensation and arrhythmia. Combined mitral lesions were the most common changes with 67 patients and other mitral lesions in 25 patients, compared with aortic lesions in 16, and double lesions in 28.

The plasma concentrations in all the digitalized patients have been given in Fig. 38. The vast majority of the patients had received digoxin. The therapeutic range of digoxin with our method is estimated to be 1.00-2.00 nmol/l; that for cedilanid, 0.70-1.40 nmol/l. With reference to the therapeutic range the patients were underdigitalized. This is an important point for two reasons. First, it is obvious that our conventional dosage of digitalis glycosides does not produce a digoxin concentration in the so-called therapeutic range. And, second, the low frequency of decompensation symptoms at the review suggests that in most cases treatment with digitalis was neither satisfactory nor necessary. Plasma levels indicating intoxication occurred in only 3 patients. In the present material digitalis intoxication was relatively rare. These findings are below the digoxin levels usually reported in the literature. It is, however, a well known fact that combination with quinidine may cause digitalis intoxication at lower plasma levels.

G. Immunological findings

The occurrence of AST in the material is given in Fig. 39. It is clear from the figure that mitral lesions were most common among patients with a positive AST,

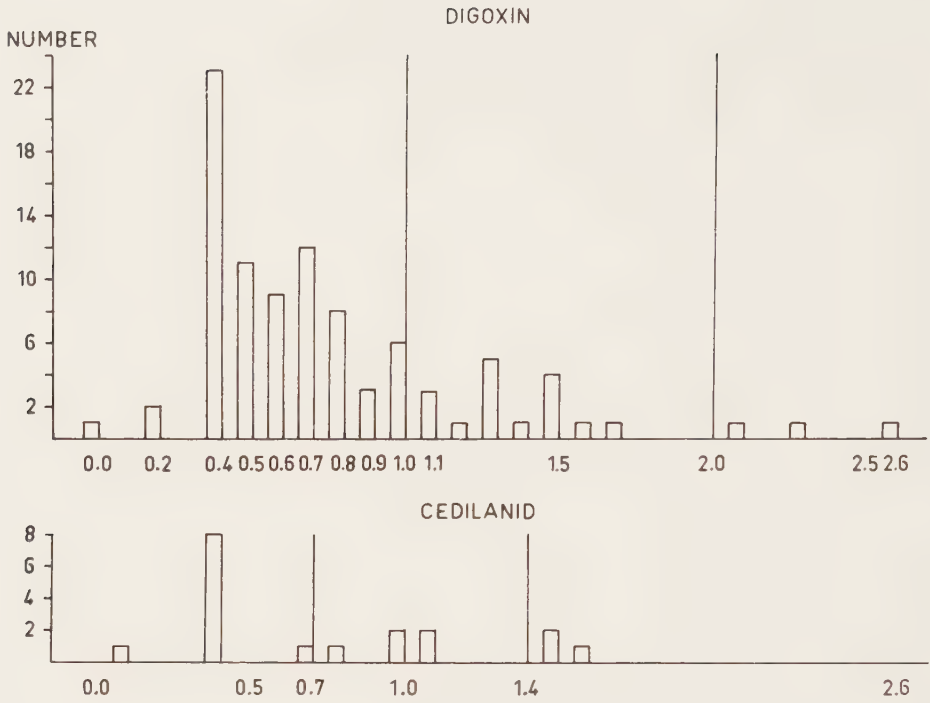


Fig. 38 Blood digoxin levels in patients using digoxin or cedilanid.
Vertical bars denote therapeutic range.

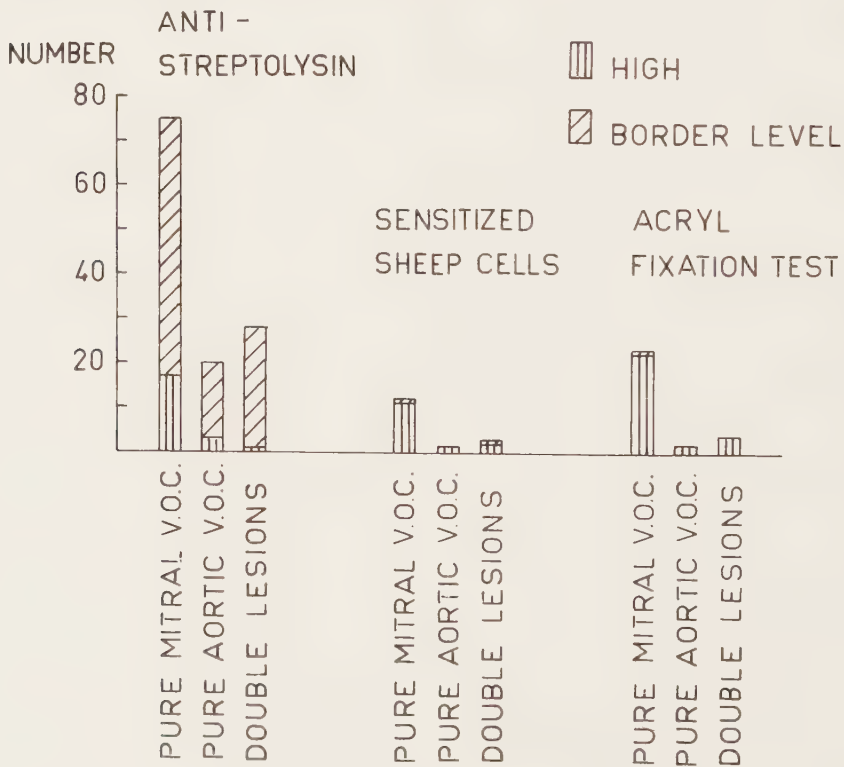


Fig. 39 Serological tests.

and of those with an isolated lesion of the mitral valve the AST was increased in 17 and showed a borderline value in 58, while the AST values in the remaining patients with lesions were low. The borderline values, i.e. under 225, were somewhat more common and most common in patients with mitral lesions. This may suggest a slightly increased tendency of patients with rheumatic mitral valvular defects to have a decreased resistance to streptococcal infections. The patients with mitral lesions in our study also had a higher frequency of a history of rheumatic fever.

As for the Waaler-Rose test, patients with isolated lesions of the mitral valves were predominant with 11 patients positive, i.e. at least 32. The same tendency was found for the acryl fixation test, which showed increased values for 22 patients. The patients with mitral lesions thus tend to have high serological titres of both rheumatoid factor and AST. Eight per cent of the VOC patients had a high Waaler-Rose test, compared with less than 4 % in a general population, possibly arguing for a slight connection between rheumatic valvular disease and rheumatoid arthritis, as measured with the rheumatoid factor. The occurrence of a higher frequency of antigammaglobulin in the VOC patients may be connected with a stronger tendency to autoimmune response.

Also the acryl fixation test suggested the existence of such a connection.

VII. ECG changes in patients with lesions

ECG changes were interpreted in accordance with the Minnesota Code. Left axis deviation of the heart was noted in 15 of the patients with mitral stenosis and 7 of the patients with mitral incompetence. The numbers for aortic stenosis were 8 and for aortic incompetence 2. For bivalvular lesions the number was 14. Right ventricular hypertrophy was rare.

Signs of infarction were observed in 3 patients with mitral lesions and in 2 with aortic defects and ST-T changes suggesting coronary insufficiency (or effect of digitalis) were also rare and seen in only respectively 5 and 3 patients. A PR-interval longer than 0.21 seconds was diagnosed in all together 10 patients with mitral damage and in 1 with an aortic lesion. Pre-excitation, Wenckebach's periods and sino-auricular block were not observed in any patient. Neither was AV block of the 2nd or 3rd degree.

As expected, atrial fibrillation was common among patients with mitral lesions, namely in 64 of 171 and a further 12 had atrial flutter. Twenty of the 80 with aortic lesions had fibrillation or flutter. Sick-sinus syndrome and bradyarrhythmia have recently attracted considerable attention. Technical and economic facilities for continuous long-term ECG tape-recording were not available in the present investigation, but resting 5-minute ECG recordings were made. Only two new cases of the sick-sinus syndrome were diagnosed.

Ventricular extra systoles were noted in 43 patients with mitral lesions, including 23 with combined mitral lesions. Of the patients with aortic defects, 20 had ventricular extra systoles. The number of ventricular extra systoles in patients with such extra systoles during the 5-minute recording were 21.3 in those with double lesions, compared with 17.9 and 10.5 in those with aortic and mitral lesions, respectively.

The number of supraventricular extra systoles in patients with extra systoles were 2.3 per 5-minutes in those with mitral valvular lesions, 6.3 in those with aortic lesions and 3.4 in those with double lesions. In patients with ventricular extra systoles the number was thus relatively high, possibly suggesting an increased irritability of the ventricular walls.

A. Pacemakers

During the period in question pacemakers were implanted mainly because of A-V block and Adams-Stokes' syndrome. Only 5 VOC patients had been treated with a pacemaker, i.e. too few to warrant any detailed analysis. In Malmö the actual frequency of pacemaker implantation was 120 per million inhabitants per year. This number is therefore above the average. Valvular lesions thus more often had an indication for implantation of a pacemaker.

VIII. Spirometric findings in patients with rheumatic lesions

All the patients with rheumatic lesions were arranged according to age, and every fifth one was examined with spirometry and blood gas analysis, Fig. 40-42, according to Sundström (312) and Larsson et al. (194) respectively. On the whole, the findings made with each method in patients with aortic lesions, mitral lesions and combined lesions differed very little from normal, suggesting that lung function was not affected to any noteworthy extent. A moderate reduction of vital capacity and increased residual volume as well as some decrease in FEV_1 were found in those patients with usually treated lesions in whom the decompensation had been controlled. Detailed analysis of the findings in each group separately revealed nothing to modify the above overall picture.

The vital capacity was lowest (70 %) in patients with isolated mitral stenosis, and the residual volume was largest (138 %) in patients with combined mitral defects, FEV_1 was lowest (76 %) in patients with mitral stenosis and FEV_1/VC was lowest (74%) with mitral insufficiency. PaO_2 was lowest and $PaCO_2$ highest in mitral stenosis, where also the pHa was lowest (7.44).

Generally speaking, the values were somewhat better for non-smokers. This is in accordance with many reports, among others, those from the department of clinical physiology in Malmö.

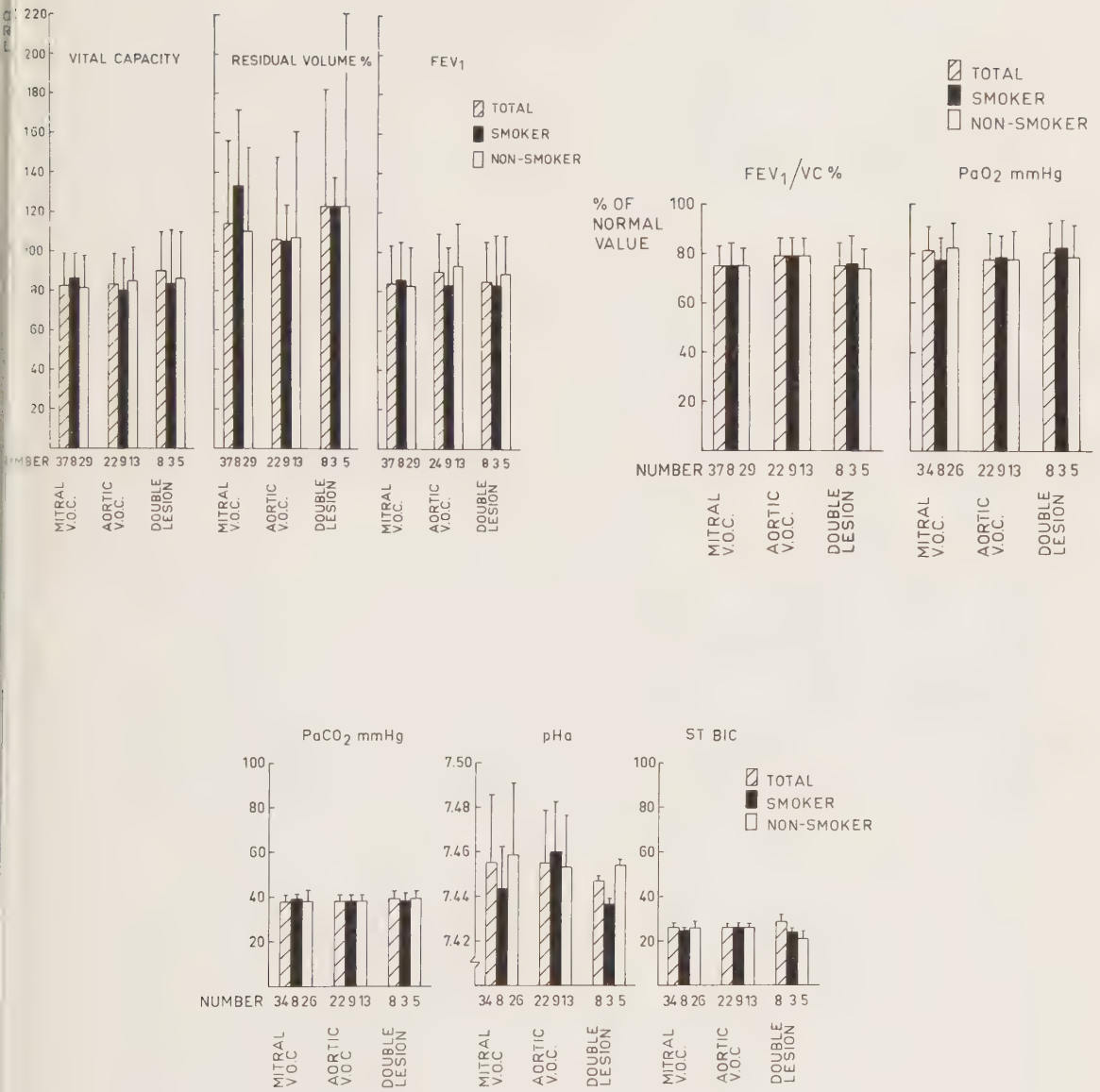


Fig. 40-42 Spirometric findings.

IX. Medical history after diagnosis

In the majority of the 206 living patients the first symptoms of heart disease appeared 4-5 years after the diagnosis of the condition (Fig. 43). In patients with a double lesion the symptoms appeared somewhat later. All the 14 patients who had developed pulmonary oedema had mitral lesions and in them the oedema had appeared 4 years after the diagnosis of the valvular lesion. The 2 patients who also had aortic lesions developed pulmonary oedema earlier than the others.

Operations for heart lesions were done, on the average, 4 years after diagnosis of the damage, but those with combined lesions were operated upon somewhat later than the others. The interval between the diagnosis and catheterization was largely the same, since catheterization was normally part of a preoperative examination or investigation of the advisability of such an operation. Ninety-six patients were examined in this way, but only 58 were subjected to operation.

When the patients with heart failure were grouped according to the affected ventricle of the heart, it was found that shortness of breath as a symptom of disease of the left of the heart appeared, as a rule, after 8 years. All together 121 patients had this symptoms, including 38 of the 73 with aortic lesions and 103 of the 170 with mitral lesions. Swelling of the legs as a sign of disease of the right side of the heart appeared about 6 years after the diagnosis of aortic lesions and 7½ years after the diagnosis of the mitral lesions.

Disturbances of rhythm, initially in the form of palpitations, sometimes extra systoles, were noticed by the patients after, on the average, 7 years. In this respect there was no difference between those with aortic lesions and those with mitral lesions, the symptom being reported by about half of each group. Of the 112 patients who had had palpitations, 48 were treated with cardioversion and then for the first time, on the average, 6 years after diagnosis of VDC. As for cerebrovascular lesions, it was not possible retrospectively to differentiate between cerebral hemorrhage, embolism and thrombosis, for which reason they were all lumped together as vascular lesions. Of the 206 patients, 26 had had this complication, i.e. one in every 8. The complication occurred about 7 years after diagnosis.

In the 133 patients taking digitalis the treatment had been started 6½ years after the onset of the disease. Treatment with diuretics had been started later and, strangely enough, treatment with digitalis and with diuretics had been started later in patients with double lesions. All together 41 patients had double lesions and 28 of them were taking digitalis and 24 diuretics.

Hypertension started according to anamnesis much later, on the average, 11 years after the diagnosis of the heart damage. Five patients had a pacemaker - 2 of them with aortic lesions very soon after the diagnosis of the lesion. Also 2 patients without lesions had a pacemaker.

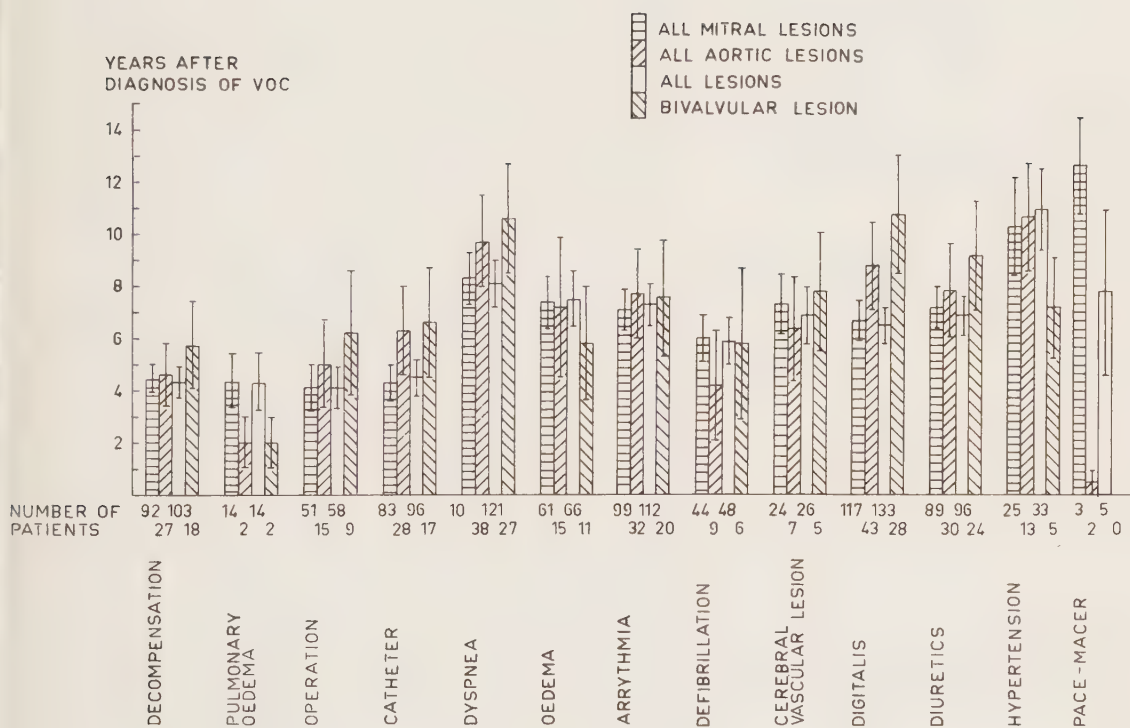


Fig. 43 Interval between diagnosis and complications.

X. Complications

A. Interval between onset of symptoms and diagnosis

The interval between the onset of symptoms and the diagnosis of the lesions in the entire series was relatively short (Fig. 44). The symptoms appeared earliest in the group with aortic insufficiency and combined aortic lesions, and latest in the group with stenosis of the mitral valves and double lesions. All the patients who developed heart failure did so, on the average, within 6 years of the diagnosis. In patients with aortic incompetence or combined aortic lesions swelling of the legs and breathlessness occurred earlier than in the other group and took, on the average, about 3 years to develop. Patients with mitral insufficiency and aortic stenosis developed oedema in the legs much later, i.e. after 20 years. Oedema in the legs, however, tended to occur earlier than shortness of breath in patients with double lesions as well as in patients with aortic insufficiency or combined aortic lesions.

B. Working capacity

The working capacity of patients with heart lesions is important from a socio-economic point of view. About half of the patients with aortic or mitral lesions were unable to manage full-time or part-time work. The corresponding figure for conditions other than cardiac defects was less than 10 %.

The number of patients with working incapacity is shown in Table IV.

The mean ages of the groups that had stopped full-time employment, part-time employment or/and had no longer been capable of doing housework were roughly equal for the different types of lesions (Fig. 45). Generally speaking, in the patients with rheumatic lesions, irrespective of type, who were unable to cope with full-time employment the age of 53-56 was most often the age when these problems appeared to become critical. The corresponding age for part-time employment was 55-57, and for household work 59 years. Patients with a double lesion often managed somewhat better. A sick-pension had been granted somewhat earlier in the group with mitral lesions than in the group with aortic lesions, namely 53 and 56 years, respectively. It is difficult to give any reliable figures for the interval between the diagnosis of rheumatic lesions and the beginning of reduction in working capacity (Fig. 46), since some patients never experience any such handicap during their active years of life. As for the handicapped patients with mitral lesions alone or combined with some other defect, the interval between the diagnosis and inability to cope with household work was 6 years, while the corresponding interval for part-time and full-time employment was 8 years after the diagnosis of valvular disease. One hundred and eleven patients could no longer cope with housework. Fifty-five patients had been granted a sick-pension after an interval of 9 years. These figures were about the same for the

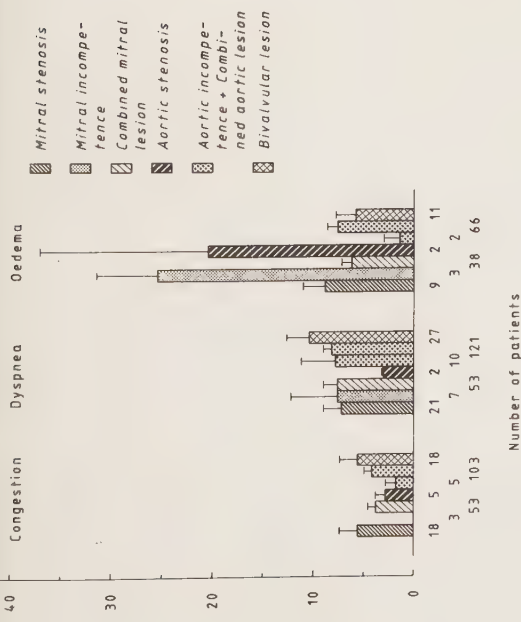


Fig. 44 Age distribution of complications of rheumatic heart disease.

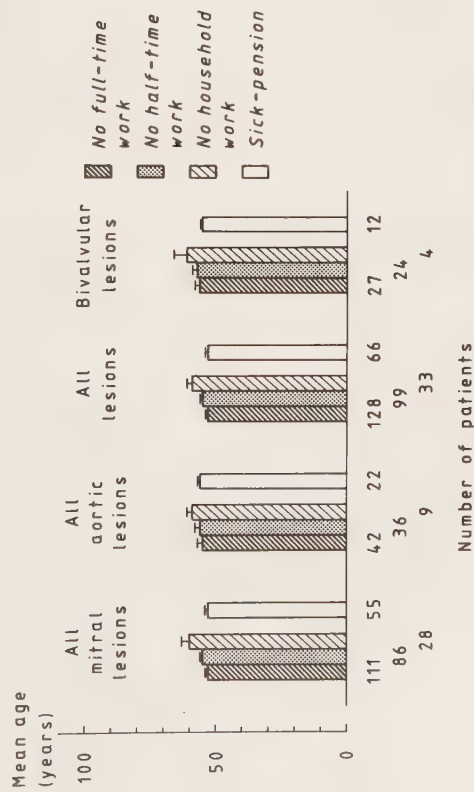


Fig. 45 Age distribution of loss of working capacity.

Type of lesion

Pure mitral	Pure aortic	Bivalvular	Other
43	14	14	-
19	3	2	1
35	7	15	-
18	5	4	-
11	2	5	-

Manages full-time work
Manages only half-time work
Manages only household work
Manages no household work
Other cause for impairment

Table IV Patients with cardiac lesions. Impairment of working capacity.

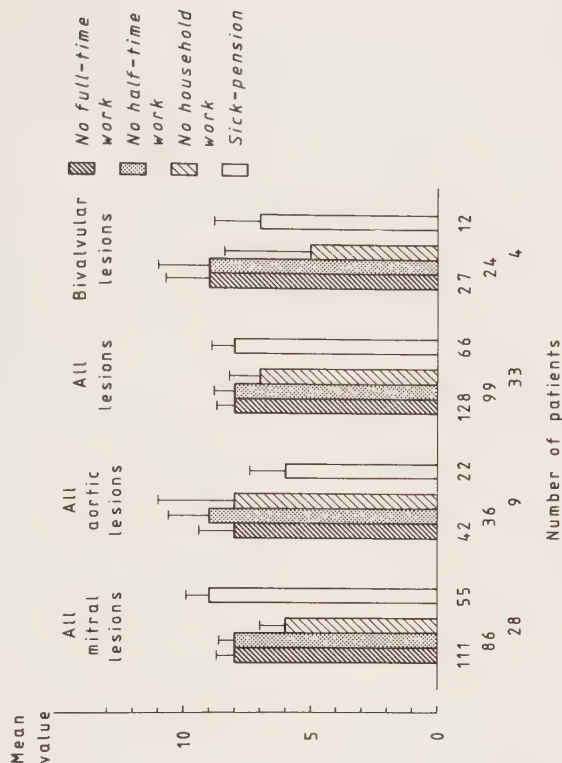


Fig. 46 Interval from diagnosis to loss of working capacity.

patients with aortic lesions, except that the latter could manage housework somewhat longer, an observation in agreement with the conception that these are handicapped somewhat later than those with mitral disease. The 22 patients with aortic lesions and receiving a sick-pension had been granted a pension after a shorter interval, viz, on the average, after 6 years.

In the entire group with rheumatic lesions the patients were no longer capable of coping with full-time or part-time employment after, on the average, 8 years. For those with a double lesion the interval was 5 years, but the range of variation was wide.

In Hall's material half of the patients could continue to work full-time, compared with only one fourth in the present series (Fig. 47). This difference can be explained partly by the fact that all of Hall's patients with lesions had had rheumatic fever, while the present series included also patients with lesions without rheumatic fever in their history, and partly by the difference in the time the diagnosis had been made, with the result that patients who were seriously ill in Hall's material could have died before our review.

From 1969 the law was changed and sick-pensions were granted fairly generously, especially for patients over 60 years of age. During the period in question all persons were entitled to an old age pension at the age of 67, people working in certain trades or professions, at 65. One hundred and thirty of the present patients, including 4 who were very young, were unable to work at all and had been granted a sick-pension, most often because of rheumatic lesions. As far as occupation is concerned, then, rheumatic valvular disease is often an incapacitating condition (Fig. 48).

XI. Fertility

A question often discussed is whether or not pregnant women with rheumatic valvular disease should be advised to go on to term or to have an abortion and whether female patients with such lesions should be advised to avoid pregnancy. Of our female patients (Fig. 49), 114 patients had children of their own and 27 had not.

Only 12 - 6 with aortic defects and 6 with mitral valvular defects - had undergone abortion and 9 had been sterilized. It would thus appear that in most patients without serious symptoms there is no reason why reproduction should be regarded as contraindicated by such lesions. No difference in fertility was demonstrable between those women who had had rheumatic fever and those who had not.

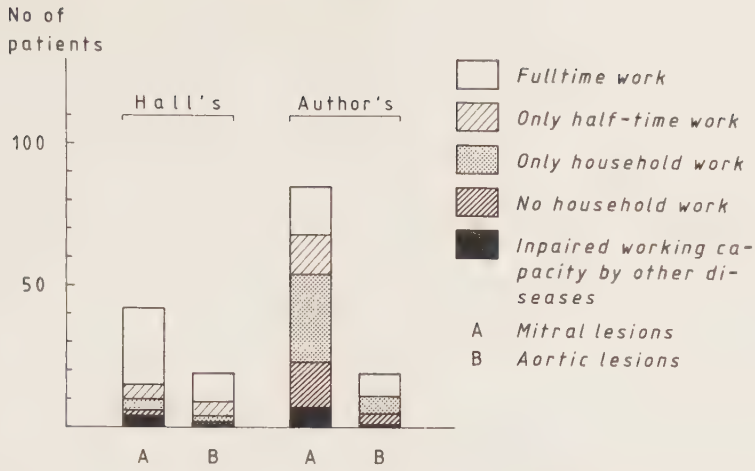


Fig. 47 Comparison of working capacity in the two materials.

SICK-PENSION

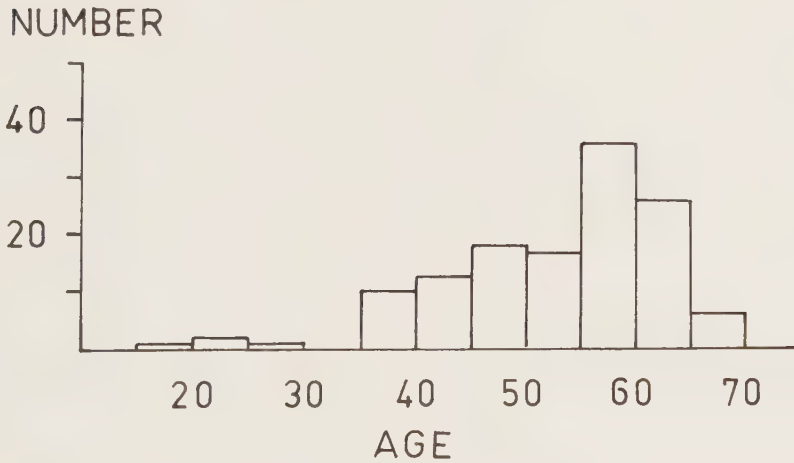


Fig. 48 Age distribution of patients at time granted a sick-pension.

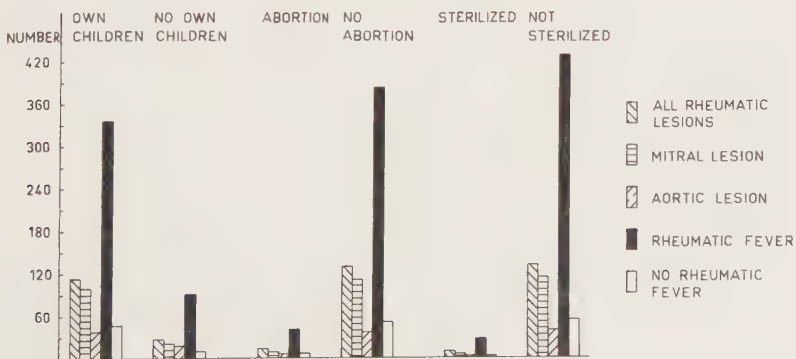


Fig. 49 Frequency of fertility in rheumatic heart disease and rheumatic fever.

CHAPTER VIII

RADIOLOGICAL FINDINGS IN PATIENTS WITH CARDIAC LESIONS

Authors: Bertil Persson and Peter Aspelin

The cardiac and pulmonary changes in the patients with rheumatic fever and those with VOC were evaluated from ordinary chest films obtained in AP (anterior-posterior) and lateral views. The films were taken at the follow-up study and were evaluated jointly by both authors, who were unaware of the clinical diagnosis. The radiological diagnoses were later correlated to the clinical diagnoses. Both the author's patients and those with rheumatic fever and examined by Hall, all together 825, were investigated. Chest films obtained at other hospitals were examined in collaboration with the local radiologist. Eighteen patients were interpreted only by the local radiologist.

Any enlargement of the heart or its chambers was graded as mild, moderate or severe.

I. Radiological findings

These are shown in detail in Fig. 50-51, and do not differ to any remarkable extent from what was expected.

A. Mitral lesions

Mitral stenosis

Of 28 patients with mitral stenosis, changes were found in 26. As expected, left atrial enlargement dominated, followed by enlargement of the right ventricle.

Mitral incompetence

Of 16 patients with isolated mitral incompetence, changes were demonstrated in 11. Here, too, enlargement of the left atrium dominated.

Combined mitral lesions

Changes were seen in 76 of 82 patients with combined mitral lesions. Most had enlargement of both the left atrium and ventricle. Aortic changes were more common in cases with combined mitral lesions than in those with other valvular lesions.

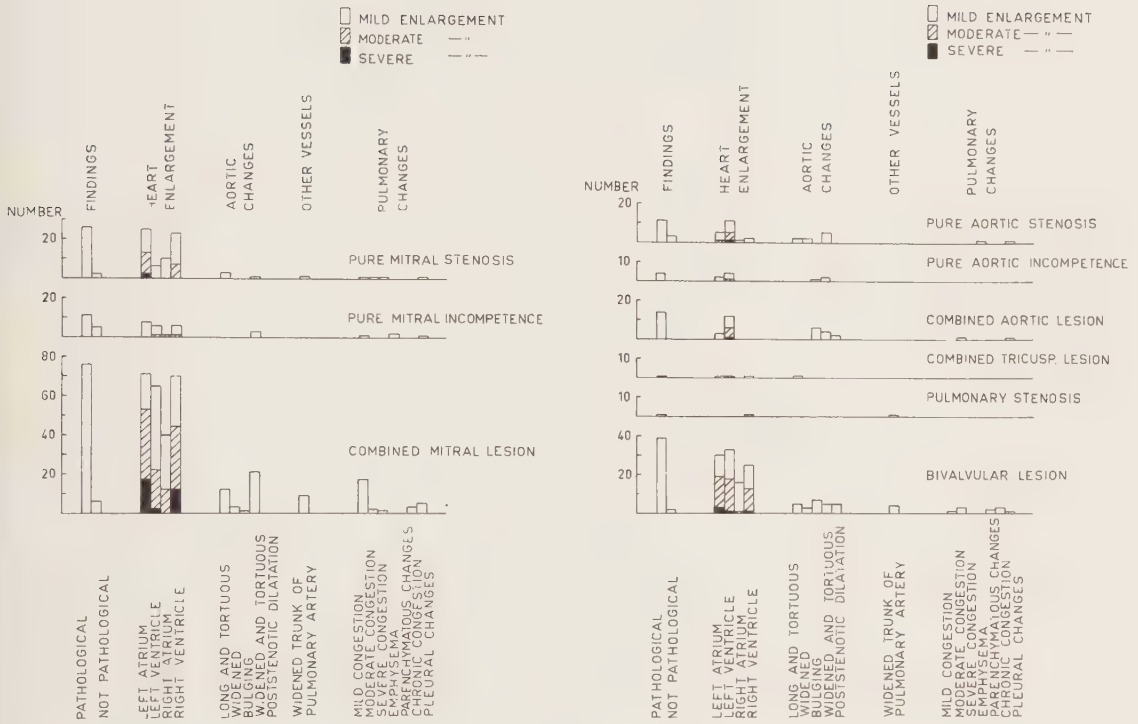


Fig. 50-51 Roentgenological findings in patients with rheumatic heart disease.

B. Aortic lesions

Aortic stenosis

Of 14 patients with isolated aortic stenosis, enlargement of the heart was found in 11. Enlargement of the left ventricle dominated.

Aortic incompetence

The chest film revealed changes in all 4 patients with aortic incompetence. The left ventricle was slightly enlarged in 3 patients and moderately so in 1.

Combined aortic lesions

Radiological changes were seen in all 14 patients with combined aortic lesions. The left ventricle was enlarged in 12, the enlargement was severe in 1, moderate in 5 and mild in 6 patients.

C. Bivalvular and other lesions

Of 41 patients with double lesions, i.e. involvement of both the aortic and mitral valves, 30 showed radiological changes and in 2 patients the chest films were normal. The left atrium was enlarged in 30 patients.

D. Heart volume

In both women and men with lesions, irrespective of type, the heart volume was increased, as judged with Jonsell's (164) method; 812 patients were evaluated. The enlargement was greatest in patients with combined mitral changes (men 1420/760 ml/m² body surface, women 1230/750) and double lesions (men 1400/760, women 1270/790). The ratio was the same in both sexes. The smallest volumes were found in patients with combined aortic lesions (men 1120/590, women 790/500). The exact values for relative heart volumes are given in Fig. 52.

E. Comparison between clinical and radiological diagnoses

The clinical diagnosis and the radiological diagnosis were made independently of each other. The agreement was regarded as good when the radiological findings corresponded well to the clinical findings. It was regarded as probable when the radiological findings were highly suggestive, but not definitely conclusive. It was regarded as one common lesion when the lesions had involved both the aortic and mitral valves, but only one of them could with certainty be diagnostically established by the chest films. For example, in patients in whom one of the lesions had involved the aorta, the radiological changes were sometimes so marked that they masked other changes produced by another lesion. It is obvious from Fig. 53 that there was good agreement between the clinical and the radiological diagnosis in 76 % (347/459) in the total material and probable in 2 % (10/459). In 12 % (56/459) there was one common lesion and in 10 % (46/459) there was

RELATIVE HEART VOLUME
ml/m² BODY SURFACE $\pm$ S.D.

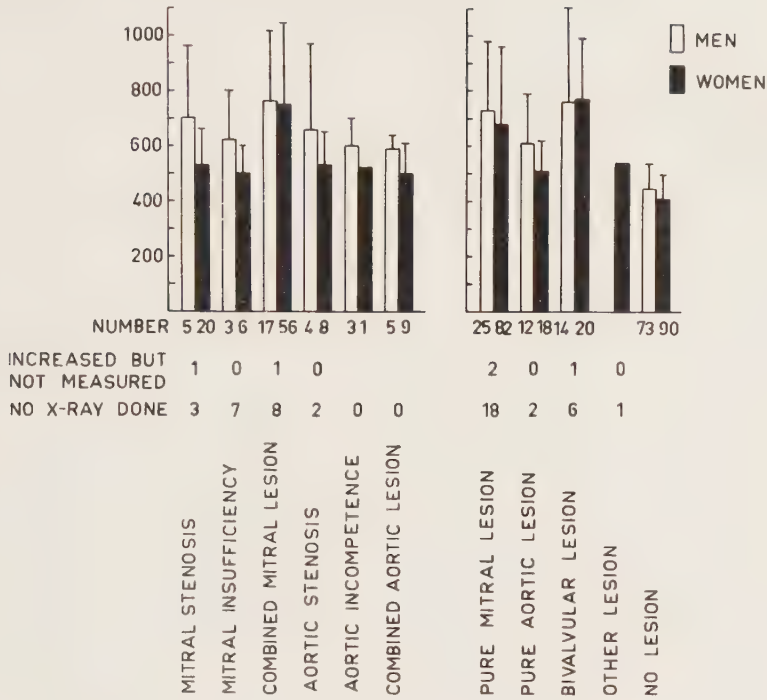


Fig. 52 Heart volumes in various kinds of rheumatic lesions.

No of patients

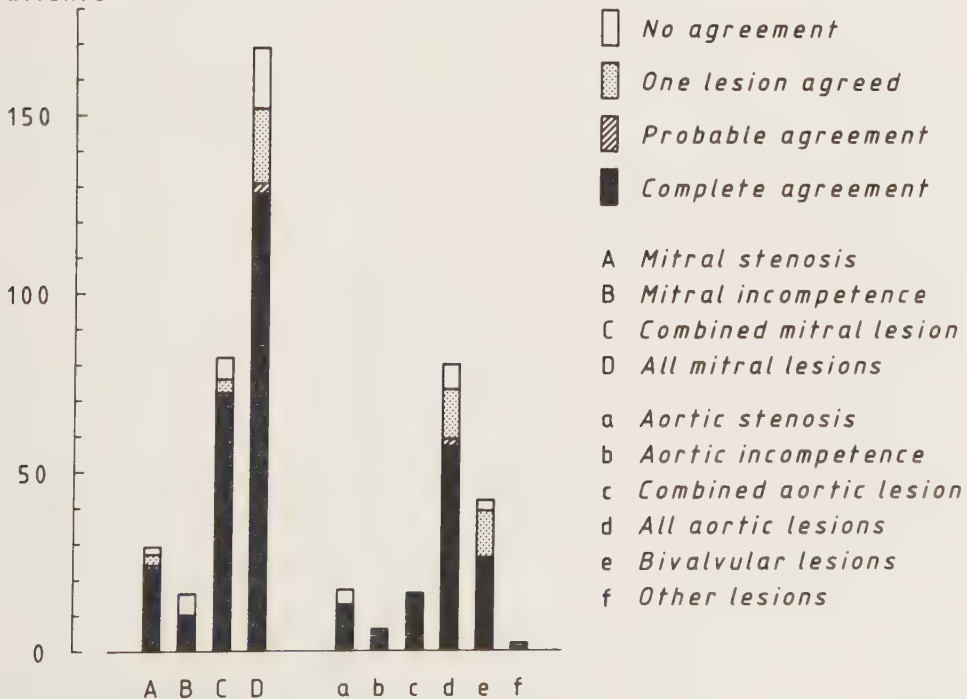


Fig. 53 Agreement between clinical and roentgen findings.

no agreement. The patients in whom the chest films did not reveal any lesion were all in an early clinical stage. We therefore conclude that the results of the two methods can be regarded as satisfactory.

II. Cineradiography of the heart

A. Calcifications in the heart

At the review the patients were examined also with cineradiography to assess the extent of calcifications in the heart and the valves as the ordinary chest films are less reliable for this purpose. The cineradiography was performed with a high speed camera which was mounted on a 9/5" X-ray intensifier (Philips XG 2010/20). The exposures were made with the aid of a cinepulse unit. The exposures were made at between 90 and 110 kv. The cineradiograms were obtained at a speed of 50 frames per second. In all, 595 patients with and without lesions were examined with cineradiography. Patients examined at their local hospitals were not examined with cineradiography. In addition, some patients declined to cooperate in this new examination. The camera was out of order some of the days and some patients were not willing to take part in a re-examination. The loss of the patients was, however, equally distributed in the material. Of the 595 patients investigated, 119 showed changes in the mitral valves and 57 in the aortic valves, (Fig. 54). Of all the patients with mitral lesions, calcifications were found in the mitral valves in 33 % (39/119). Of patients with aortic lesions, calcifications were demonstrated in the aortic valves in 39 % (22/57) and in the mitral valves in 21 % (12/57). Of the patients with double lesions, calcifications were demonstrated in the aortic valves in 51 % (16/31) and in the mitral valves in 39 % (12/31).

Calcifications in the coronary arteries and elsewhere in the heart were rare in these groups. Calcifications of these types were demonstrated in 21 % (12/57) of the patients with mitral lesions and 14 % (9/57) in those with aortic lesions.

Of the 419 patients without lesions in the entire material studied, calcifications were found in the mitral valves in 2 % (8/419) and in the aortic valves in 5 % (20/419). It should, however, be pointed out that this cineradiographic study was performed before 1975 and before the advent of modern cesium iodide intensifying screens. The figures for valvular and other calcifications may therefore be underestimated. In an effort to assess the time of development of calcifications, all the patients with mitral and aortic lesions were arranged according to the time they had been known to have had such a lesion (Fig. 55). It was found that the calcifications were more common among patients known to have had a lesion for 15-20 years, but less common among patients who had had the disease more than 20 years. In patients with calcifications the calcifications seemed to occur rather early. There was a fairly low frequency, 7 % (41/595), of demonstrable coronary calcifications.

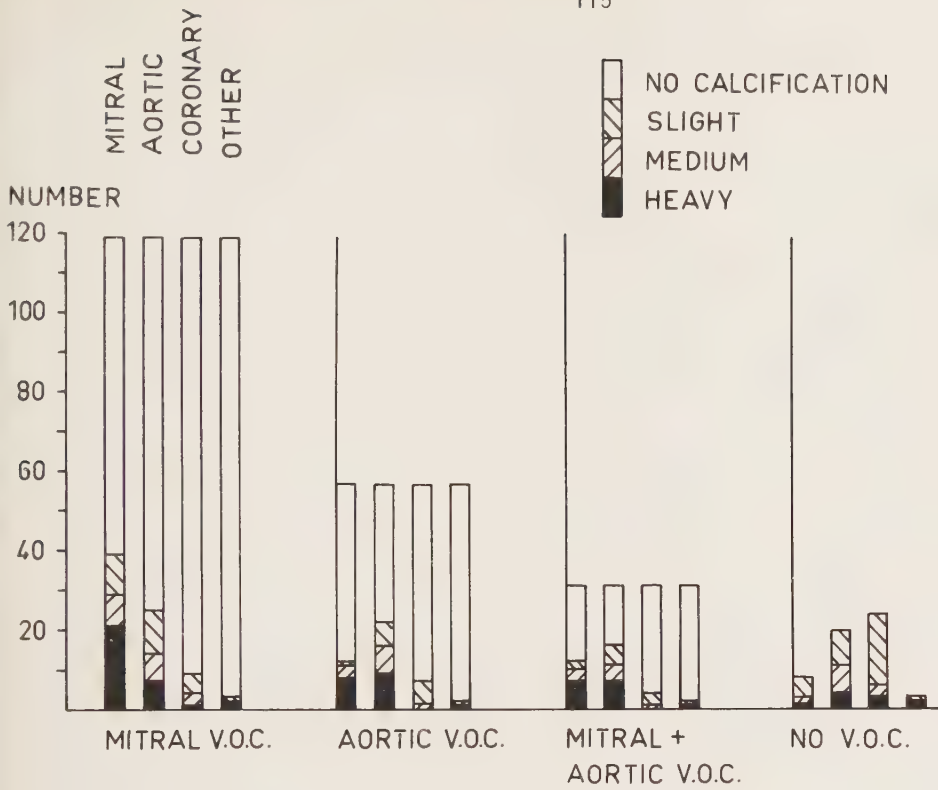


Fig. 54 Frequency of heart calcifications.

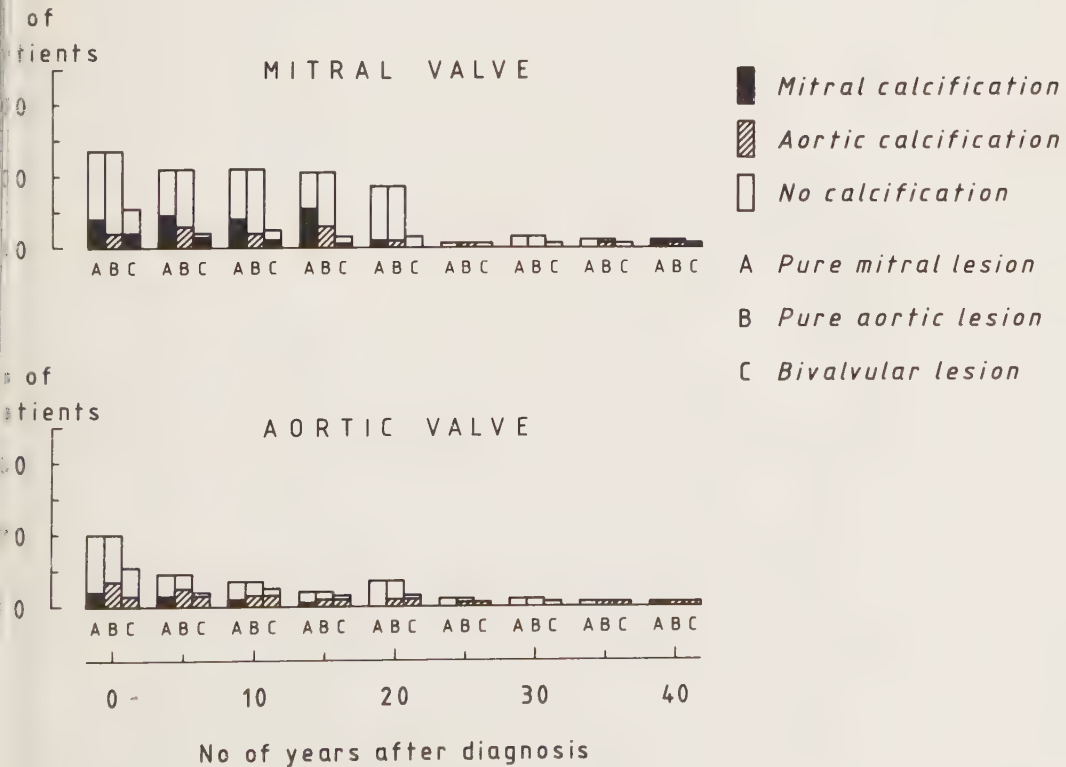


Fig. 55 Frequency of calcifications in patients at varying interval after diagnosis of rheumatic heart disease.

CHAPTER IX

RHEUMATIC HEART DISEASE - NATURAL HISTORY

I. Age factors

A. Age at diagnosis of cardiac lesions

The age at the diagnosis of cardiac lesions as well as rheumatic manifestation in patients who had had rheumatic fever is given in Fig. 56. From 1930 to 1954 all the lesions that had developed in the patients with a history of rheumatic fever were confirmed.

The age at diagnosis of the lesions was, then, possibly somewhat lower in the beginning of the study period 1930-54 than in the 1955-70 period.

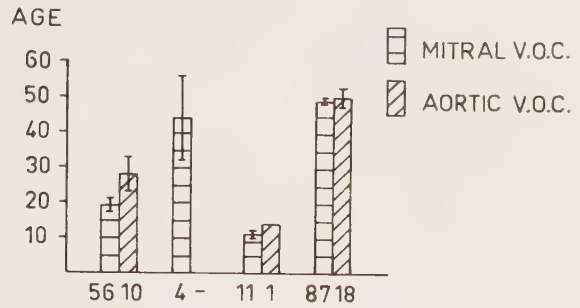
Those patients who had had rheumatic fever during the second world war (1939-44) were younger at the time of onset of the fever and the lesions had also appeared earlier in life, like those who had had rheumatic fever in 1950-55. But the trend was not striking. In view of the increasing age at onset of rheumatic fever the interval between the rheumatic fever and diagnosis of the cardiac lesions was shorter in the latter part of the material.

B. Frequency of complications and therapy

The patients were studied concerning age at diagnosis of a valvular defect, at first attack of heart failure, at heart surgery, defibrillation, cerebral hemorrhage and implantation of a pacemaker (Fig. 57). Every case is represented in the figure with each measure or symptom. It was found that the valvular lesions continuously increased from childhood with the onset at 5-10 years until a peak frequency between 50 and 55 years, but new cases were still diagnosed up to much higher ages. The curve for the first symptoms of cardiac failure was naturally of similar shape, but somewhat lower because some patients do not develop such symptoms until in later stages. The earliest operations on the heart were done on patients, aged 25-30, and were most common in 45-50-year-old patients. No patients above 60 years were operated upon in our series, because, at least at

V.O.C. PATIENTS WITH RHEUMATIC FEVER

AUTHOR'S 1955 - 70



HALL'S 1930 - 54

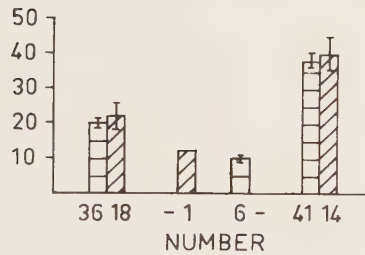


Fig. 56 Ages of rheumatic fever, rheumatic heart disease and complications in the author's and in Hall's material. Chorea occurs shortly at 10 years, rheumatic fever at about 20 years and rheumatic heart disease at about 50 years of age.

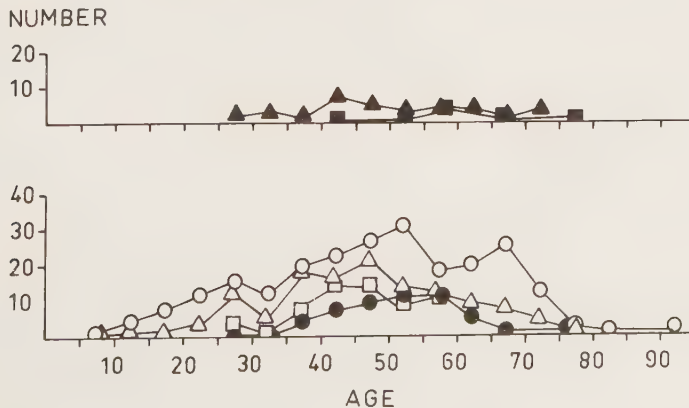
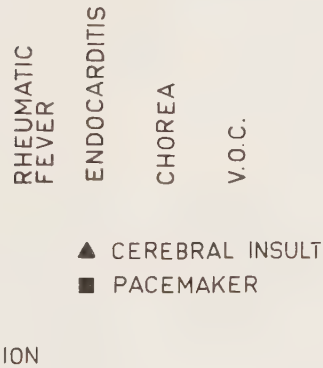


Fig. 57 Age distribution at onset of complications in total material of rheumatic heart disease.

that time, one was more reluctant to operate on the heart in elderly patients. Since the resources for thoracic surgery in Sweden are good, the fact that the frequency with which valvular lesions were treated surgically was fairly low suggests that the severity of valvular disease was not such as to necessitate operation.

Arrhythmia is a common complication of rheumatic valvular lesions and defibrillation was routinely tried to counteract atrial fibrillation or flutter. Defibrillation was done earliest in patients between the ages of 25-30 years and most often in the 55-60 year age group, but none of the patients was more than 75 years of age.

Cerebrovascular lesions are serious, but were relatively uncommon complications of rheumatic valvular lesions in our material. But such lesions occurred in some patients as young as 30-35 years. Emboli were probably the most common cause of the lesions. The relatively low frequency of such complications can possibly be explained by routine dicoumarol prophylaxis in patients with rheumatic valvular lesions combined with atrial fibrillation or flutter.

Pacemakers were not common in our material, which suggests that Adams-Stokes' attacks and complete heart block were not particularly common.

1. Material of VOC in 1955-70

In order to compare the natural history of the cardiac lesions in the 1955-70 period with that in Hall's thesis, we made a special study of these re-examined patients (Fig. 58).

We reviewed these cases. There is no great difference between the two populations of lesions re-examined. The peak incidence of diagnosis of lesions was between 35 and 55 years of age. Signs of complications followed this curve relatively closely. Oedema as an overall sign of decompensation appeared early, but dyspnea as well as oedema of the legs showed a peak between 50 and 55 years of age. Catheterization and operation reflected the still high frequency of VOC and operation in the material. Only five of the patients with a pacemaker belonged to this material. Thus no noteworthy difference was found between the 1955-70 material and our total material.

C. Therapy

Treatment of aortic and mitral lesions

The material was divided into two groups according to whether the patients had mitral or aortic damage, also when the lesion was part of a double lesion.

The figures in Fig. 59 denote how long the patients had had the lesion. The investigation showed that quinidine had rarely been used in patients with a

- V.O.C.
- △ OEDEMA
- PULMONARY OEDEMA
- DYSPNEA
- OEDEMA IN THE LEGS

- DEFIBRILLATION
- △ CATHETER
- OPERATION
- CEREBRAL INSULT
- PACEMAKER

NUMBER

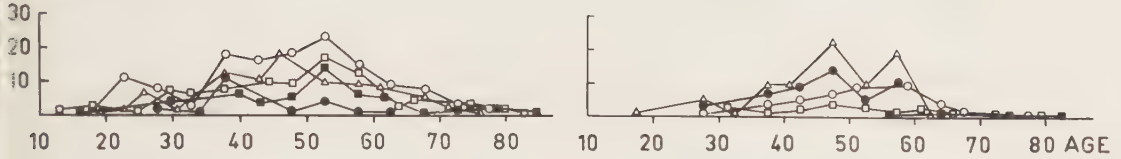


Fig. 58 Natural history of rhe re-examined patients with the first diagnosis of rheumatic heart disease in 1955-70.

■ TREATED PATIENTS

ALL MITRAL LESIONS

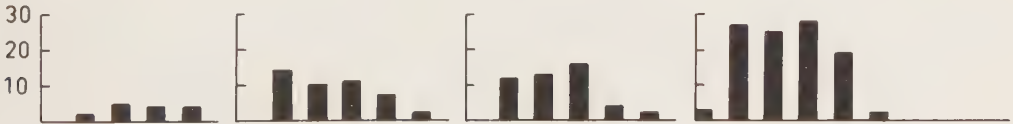
QUINIDINE

DICOUMAROL

OPERATION

DIGITALIS

NUMBER



ALL AORTIC LESIONS

QUINIDINE

DICOUMAROL

OPERATION

DIGITALIS

20

10

05 10 15 20 25 05 10 15 20 25 30 05 10 15 20 25 30 05 10 15 20 25 30 35 40

YEARS AFTER DIAGNOSIS

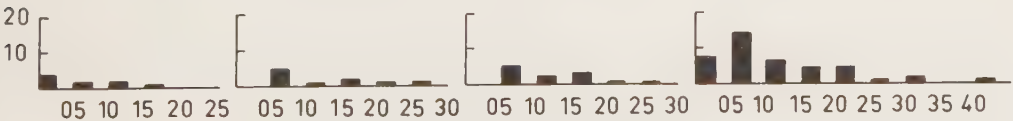


Fig. 59 Interval between diagnosis of heart disease and treatment for mitral and aortic lesions.

mitral or aortic lesion. Calculated from the time of diagnosis of the lesion, it was given somewhat earlier, or mainly during, the first 10 years in patients with aortic lesions, but after 10-25 years in the patients with mitral lesions. This agrees well with the figures for implantation of a pacemaker, but not with anamnestic data on arrhythmia.

Dicoumarol was usually given when the patients developed atrial fibrillation or flutter. None of the patients received such treatment during the first 5 years after diagnosis, but one third of those who had had mitral damage for a longer period did, and already in the group followed up for 5 years, about half were given dicoumarol, suggesting that atrial fibrillation is a fairly early complication in such cases. Patients with aortic lesions did not have dicoumarol so often. Only 10 of 69 of the patients with aortic lesions were treated with dicoumarol, compared with 44 of 134 with mitral lesions.

Operations for mitral and aortic lesions were done 5-30 years after onset, though mostly between 5 and 20 years. None of the patients were operated upon within the first 5 years after diagnosis of the condition.

Digitalis had been used very often and almost half of those with aortic damage and one sixth of those with mitral damage had started using digitalis within 5 years of the diagnosis. Most of those patients reviewed after 5-25 years, i.e. the majority of patients with mitral damage, were digitalized. Of those with aortic damage, more than half were taking digitalis.

1. Comparison between treated and untreated patients

Patients treated with surgery tended to suffer more than untreated patients from shortness of breath (inability to ascend three flights of steps without stopping) and from oedema of the legs and the social complications combined with a sick-pension (Fig. 60).

As expected, most patients with shortness of breath, oedema, or receiving a sick-pension were taking digitalis. This also applies to diuretics.

As for anti-arrhythmic treatment, only a small proportion of these patients had symptoms of cardiac failure in the form of breathlessness, or oedema and only few were receiving a sick-pension.

The duration of survival from the time of the diagnosis up to the review of patients with mitral lesions and aortic lesions, respectively, was the same for patients left untreated as for those treated with surgery, digitalis, quinidine or dicoumarol.

D. Frequency of heart surgery

In the total material, i.e. all the patients with rheumatic lesions, the frequency of heart surgery increased continuously up to 1970 (Fig. 61). The

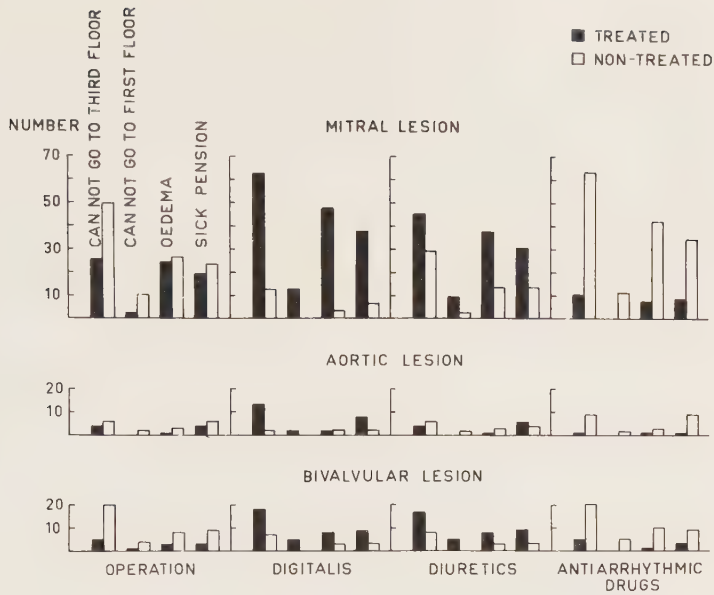


Fig. 60 Symptoms and sick-pension in patients with and without treatment.

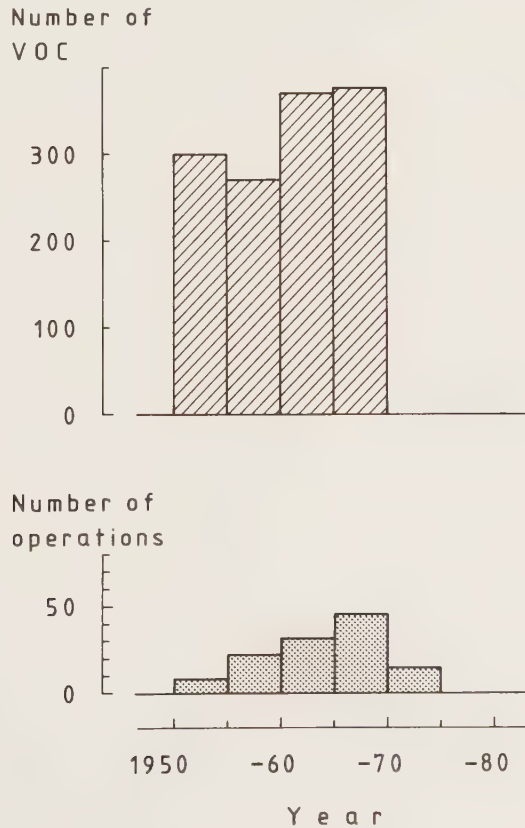


Fig. 61 Increased number of operated patients with the number of new diagnoses of VOC.

figures before 1950-55 do not represent the total number of patients with lesions, while the later figures do. The analysis must therefore be limited to the years 1955-70. Figures after 1970 include only patients in whom the lesions had been diagnosed before 1970 and who were afterwards operated upon. The increase in the figures does not reflect an increase in the frequency of serious valvular damage, but rather increased possibilities of treating such lesions surgically. Our material does, however, suggest that the relative stabilization of the number of diagnosed valvular lesions made in the period in question did not decrease the need of surgical treatment. Most of the operations on the patients, all residents of Malmö, were performed in Malmö until 1960. Since then some have been done in Uppsala, Lund and Switzerland. All the patients had discussed the envisaged operations with the department of thoracic surgery beforehand and the operations had been decided upon jointly by the local surgeons, cardiologists and the patients, even when the operations were performed elsewhere.

1. Prostheses

Prostheses were implanted in 3 patients with mitral damage, 5 with aortic damage and 2 with a double lesion. The double lesions got prostheses only in the aortic valve. In the patients with mitral damage or double lesions there was a tendency of heart failure to occur soon after the organic damage had been diagnosed.

In only 1 case did a cerebral insult occur.

E. Vascular lesions

The patients who had had vascular lesions were grouped according to the type of cardiac damage and rhythm. Of these patients, 7 had mitral lesions with sinus rhythm, 11 atrial fibrillation, 1 atrial flutter and of those with aortic lesions 1 had sinus rhythm and 1 atrial fibrillation. Of the patients with a double lesion, 2 had sinus rhythm, and 3 atrial fibrillation, but none had atrial flutter. Fibrillation was thus associated with a certain overrepresentation of vascular lesions, but the complication occurred also in patients with sinus rhythm.

II. Natural history of different types of lesions

A. Mitral lesions

1. Time course

The patients who had mitral lesions and had earlier in life had rheumatic fever were distributed according to the year in which the fever had occurred (Fig. 62). It was found that the later in the century the fever had occurred the older the patients at the diagnosis of VOC. In 1930-55 the mean age was 24 years at

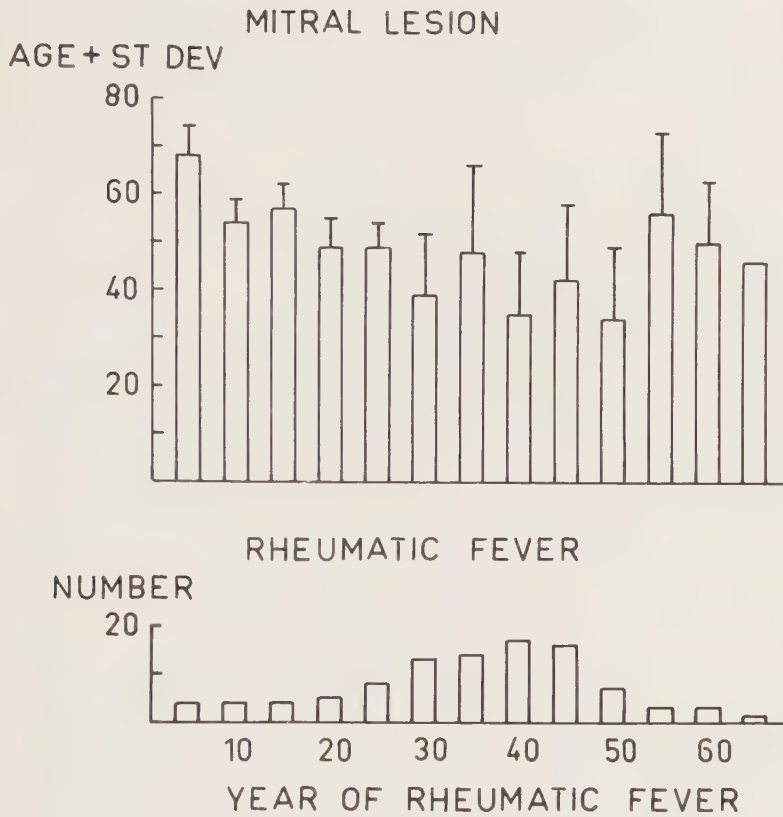


Fig. 62 Age distribution at onset of mitral lesions
(rheumatic fever material not complete before
1930).

diagnosis and in 1955-60 it was 44. Rheumatic fever with cardiac sequelae was seen in teenagers in the beginning of the century, but in the latter part of the century the victims were much older. Patients who had had mitral lesions died at 60 years of age irrespective of the time in life that the fever had occurred. Only relatively few patients who had had rheumatic fever after the advent of penicillin have died, but the material does not warrant any conclusion of an effect or lack of effect of penicillin on the duration of survival or number of patients with cardiac lesions.

2. Defibrillation and operation

The average age for defibrillation has succesively decreased, but it is still over 50 years.

All together 32 patients with mitral lesions had been operated upon (Fig. 63). It is clear from the figure that those patients who had had rheumatic fever and had been operated upon for mitral lesions were younger (as a rule about 40 years) at the time of operation than those treated surgically for aortic lesions. But there was a tendency of the age at operation to decrease in the period under discussion, probably not only because of a shorter interval between the occurrence of the lesion and the present review, but also because of advances made in cardiac surgery permitting a widening of the range of indications.

3. Course of mitral lesions from the time of diagnosis to death

It is clear from Table V that most of the patients who developed mitral lesions after having had rheumatic fever survived only a relatively short time, though some survived for as many as 50 years. As for the group without any known history of rheumatic fever, none of the patients who had died had had a history of more than 19 years from the time of diagnosis (Table VI).

B. Aortic lesions

1. Time course

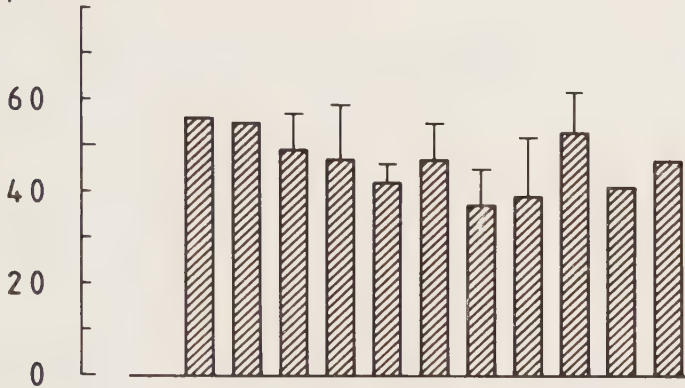
The age at onset of rheumatic fever was also analysed in patients with aortic lesions and a history of rheumatic fever. In 1930 the age at onset was 20 years compared, with 36 years in 1955-60.

But no noteworthy difference was found between the age at onset of the lesions in patients with rheumatic valvular disease in spite of the fact that the mean age at the time of the rheumatic fever had increased during the study period.

The age at death was, on the average, about 60 years irrespective of the time of rheumatic fever, but was somewhat higher towards the end of the period (1930-35 it was 64 years, 1960-65 it was 69 years). Here, too, the material was rather

MITRAL LESIONS

Age at
operation $\pm$ S.D.



Number of
rheumatic fevers

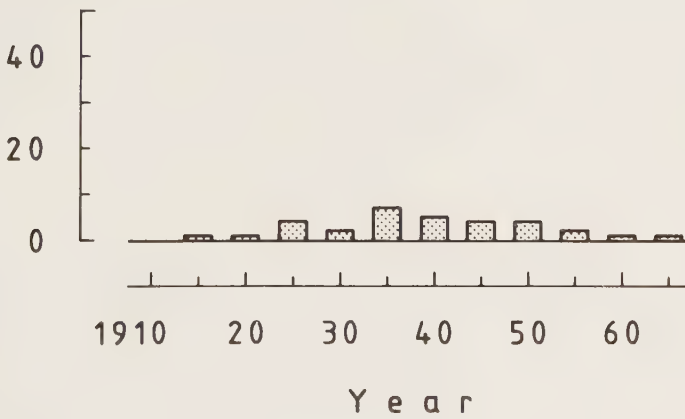


Fig. 63 Age of heart operation for mitral lesions with history of rheumatic fever.

MITRAL LESIONS, AORTIC LESIONS AND DOUBLE LESIONS - RHEUMATIC FEVER

YEAR OF DEATH MINUS YEAR OF DIAGNOSIS

55-59												
50-54	1-0-0											
45-49												
40-44		1-1-0	1-0-0									
35-39		1-0-1	3-0-0	1-0-0								
30-34			2-0-1									
25-29			1-0-0	1-0-0	1-0-1							
20-24			1-0-1		3-1-1	3-0-2	2-0-1					
15-19				1-0-0	1-1-0	2-0-3	5-0-0	4-0-0				
10-14					1-0-0	3-2-1	3-2-1	5-1-4	1-1-3			
05-09						1-1-0	5-1-5	6-2-2	8-4-3	1-0-3		
00-04							1-2-0	24-8-7	27-14-17	22-14-7	4-3-3	
	15	20	25	30	35	40	45	50	55	60	65	70
YEAR OF DIAGNOSIS												

Table V Interval between diagnosis of VOC and death in patients with rheumatic fever. Numbers denote respectively mitral, aortic and bivalvular lesions.

MITRAL LESIONS, AORTIC LESIONS AND DOUBLE LESIONS - NO RHEUMATIC FEVER

YEAR OF DEATH MINUS YEAR OF DIAGNOSIS

35-39												
30-34					0-1-0							
25-29												
20-24												
15-19	0-0-1	1-1-0		1-0-2								
10-14	0-0-1	0-0-1		7-2-2	6-3-0							
05-09				5-2-2	7-9-5	6-3-1						
00-04				61-56-23	69-113-27	91-144-39	10-22-5					
	45	50		55	60	65	70					

YEAR OF DIAGNOSIS

Table VI Interval between diagnosis of VOC and death in patients without rheumatic fever. Numbers denote respectively mitral, aortic and bivalvular lesions.

small, especially that after the beginning of the penicillin era, for which reason it is not possible to draw any conclusions about the effect of treatment with penicillin.

2. Defibrillation and operation

Only 2 patients with aortic lesions and an earlier history of rheumatic fever were defibrillated.

Three patients with aortic lesions and a previous history of rheumatic fever were operated upon, (Fig. 64). They were 49-58 years old. The group is far too small to warrant any conclusions.

3. Course of aortic lesions from the time of diagnosis to death

The duration of survival of patients with aortic lesions and an earlier history of rheumatic fever (Table V), was likewise relatively short. One patient survived 40-44 years, but most of them, 41 of 58, only up to 5 years. This is still more obvious among those who had no rheumatic fever in their history, most of them surviving less than 5 years.

C. Double lesions

1. Time course

In the patients who had had rheumatic fever and afterwards developed double lesions the age at onset of the fever rose from one decade to another. It was thus 14 years in the 1930-35 period and 28 years in the 1945-50 period. The range of variation of age at onset of the lesions was wide. If we disregard 2 cases that occurred after 1960, Fig. 65, the age at onset of double lesions was, if anything, somewhat lower.

Like aortic and mitral lesions, the average age at death was about 60 years throughout the entire study period. The number of patients in the penicillin era was small (Fig. 66), but other treatment of the lesions and of the symptoms of cardiac failure with improving methods appeared not to prolong the survival of the patients.

2. Defibrillation and operation

Only 3 patients with double lesions were treated with defibrillation between the ages of 53 and 67. The group with an earlier history of rheumatic fever and later operated upon for double lesions consisted of 8 patients, including 5 in whom rheumatic fever had not been diagnosed after 1930. Generally speaking (Fig. 67), the ages of the patients at the time of the operation were 42-56 years, and possibly somewhat lower for those who had had rheumatic fever in relatively recent years.

AORTIC LESIONS

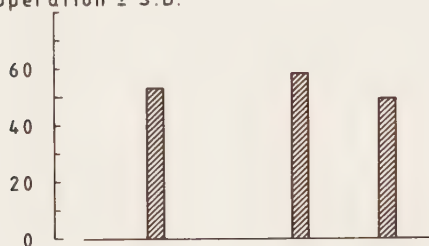
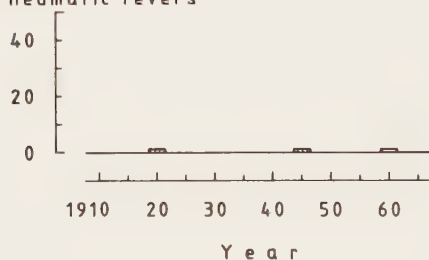
Age at
operation $\pm$ S.D.Number of
rheumatic fevers

Fig. 64 Age of heart operations for aortic lesions in patients with history of rheumatic fever.

BIVALVULAR LESIONS

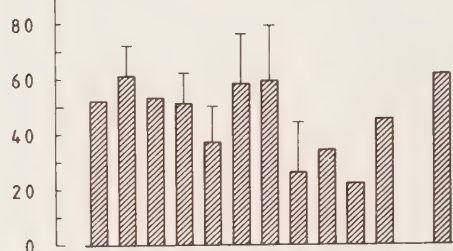
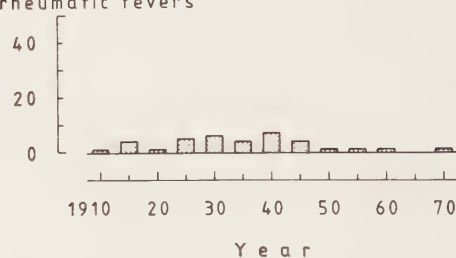
Age at diagnosis
of V.O.C. $\pm$ S.D.Number of
rheumatic fevers

Fig. 65 Age distribution at time of diagnosis of combined mitral and aortic lesions with history of rheumatic fever.

BIVALVULAR LESIONS

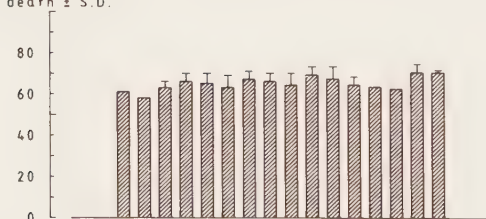
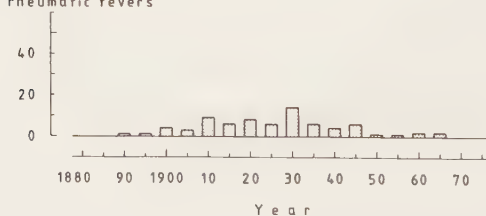
Age at
death $\pm$ S.D.Number of
rheumatic fevers

Fig. 66 Distribution of age at death among patients with combined mitral and aortic lesions.

BIVALVULAR LESIONS

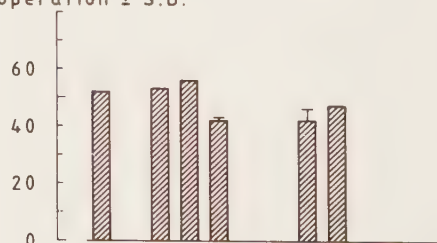
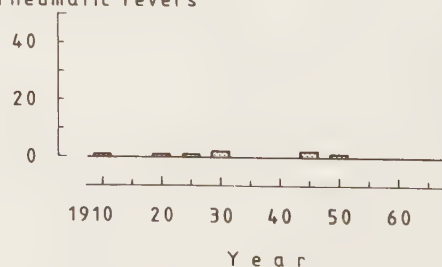
Age at
operation $\pm$ S.D.Number of
rheumatic fevers

Fig. 67 Age distribution at time of operation for combined mitral and aortic lesions with history of rheumatic fever.

3. Course of double valvular lesions from the time of diagnosis to death

In the patients who had had rheumatic fever the interval between the rheumatic fever and the diagnosis of the lesions tended to be somewhat short, as 47 of 67 had an interval of less than 10 years, but was sometimes as long as 35-39 years (Table V). In patients who had not previously had rheumatic fever the interval was increasingly often very short.

III. Interval between diagnosis and symptoms during the study period

A. Rheumatic fever series

The Malmö material was reviewed after such a long time that it was thought of interest to study the interval between the diagnosis and the appearance of symptoms. The diagnoses were distributed among 5-year periods according to the time of onset of symptoms. The results were the same for each period and for the entire study period.

Interval between rheumatic fever and complications

Valvular lesions

In patients who had had rheumatic fever, the frequency of complications of valvular lesions increased with the interval after the rheumatic fever episode. As already pointed out, the number of new cases of lesions per 5-year period after the diagnosis of the lesions was relatively constant. It is also clear from Fig. 68 that the frequency of rheumatic valvular lesions after rheumatic fever must be related to the interval between rheumatic fever and the time of diagnosis of the lesions, and that a mean interval between the appearance of rheumatic fever and the onset of lesions is only a rather artificial value, as it is so very dependent on very long observation times. This requirement of a long observation time has only rarely been met. Yet it was fairly obvious that already during the first 5-year period a diagnosis of lesions was by no means uncommon and that more lesions develop successively during the later periods.

Shortness of breath

Fig. 68 shows the interval between the diagnosis of the rheumatic fever and the onset of breathlessness, which was usually a sign of incipient failure of the left heart. Here, too, the symptom often appeared within 5 years of the diagnosis, i.e. relatively soon. Yet there was an increasing number of patients with more severe breathlessness 20-30 years after the rheumatic fever.

Swelling of the legs

It is clear from Fig. 68 that swelling of the legs indicating failure of the right heart showed the same tendency in respect of the time of its appearance as

No of
patients

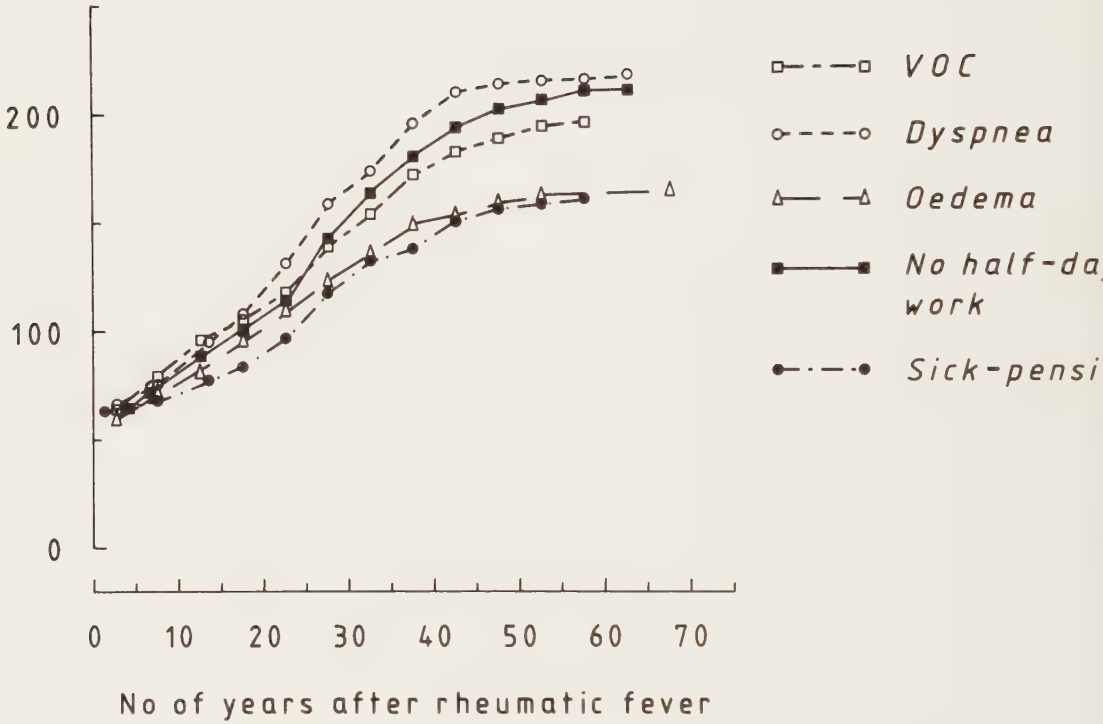


Fig. 68 Cumulative number of patients with history of rheumatic fever and complications.

did breathlessness.

Working capacity

Loss of working capacity was said to have occurred when the patient could no longer cope with part-time employment, i.e. he was incapacitated for work (Fig. 68). Here, too, the situation was the same for a considerable number of patients who were no longer able to work relatively soon after rheumatic fever, and an early onset of the lesion. During the following 5-year period the number of new cases of loss of working capacity was lower, but increased again from 25 years after the onset of the rheumatic fever, i.e. somewhat later than the onset of heart failure.

Sick-pension

Sick-pension as a sign of permanent inability to work showed the same pattern as inability to cope with a part-time occupation (Fig. 68). Generally speaking, the figures were somewhat lower, presumably because housewives who were unable to cope with a half-time job were not always granted a pension but continued to look after the house. Here, too, many were granted a sick-pension relatively soon after rheumatic fever and an early lesion, while the next largest group was found more than 25 years after the onset of the rheumatic fever, i.e. somewhat later than symptoms of heart failure.

B. Rheumatic lesions

Interval between diagnosis of lesion and complications

Shortness of breath

Shortness of breath as a sign of involvement of the left heart was a common symptom already within the first few years after the diagnosis of rheumatic lesions. The total number of cases successively increased, but left ventricular failure is obviously a very early symptom in patients who have developed a rheumatic lesion (Fig. 69).

Pulmonary oedema

Pulmonary oedema implying severe left ventricular failure was strikingly uncommon in our patients with cardiac lesions, suggesting that treatment with diuretics was at any rate effective enough to ward off pulmonary oedema in the vast majority of the cases. When pulmonary oedema occurred, it was fairly soon after the diagnosis of the lesion, possibly in association with the establishment of the diagnosis of the lesion. There was therefore hardly any accumulation of cases with time, and after 15 years there were no such cases at all, which must be ascribed to effective therapy.

No of VOC

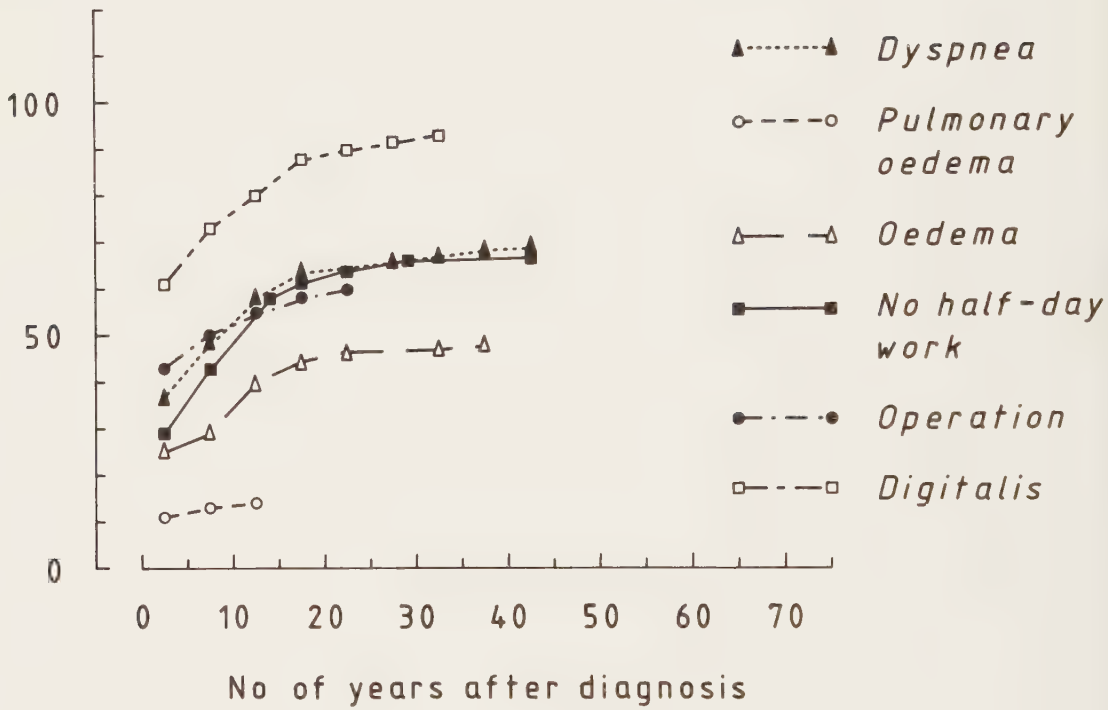


Fig. 69 Cumulative number of patients with VOC with sequelae.

Swelling of the legs

Oedema of the legs as a sign of right ventricular failure was common the first few years after diagnosis of the heart lesion (Fig. 69), but tended to be less common during the latter part of the study period suggesting that effective therapy had improved the patients' incompensation.

Working capacity

The interval between the diagnosis of the lesions and inability of the patients to cope with half-day employment is given in Fig. 68. It is clear from the figure that the incidence of such inability was high already within a few years of the diagnosis of the lesions and continued to increase successively during the following years. Separate analysis showed that the figures were somewhat higher after 1965, which need not imply a worse prognosis, but may be due at least partly to a more liberal attitude to the granting of a sick-pension.

Treatment with digitalis

The use of digitalis because of incompensation, enlargement of the heart or atrial fibrillation is very often started within a few years after the diagnosis of the heart lesion. Digitalis was used more often in the present study period than previously. The majority of patients using digitalis had started taking the drug within 5 years after the diagnosis of the lesion (Fig. 69).

Heart surgery

Most operations on the heart were performed early after the diagnosis of the lesion and then mostly within 5 years. The frequency of such operations also increased during the study period (Fig. 61). Presumably because of improved surgical facilities also in more complicated cases.

CHAPTER X

AUTOPSIED PATIENTS

I. Rheumatic fever

As shown in Fig. 28, the patients who died from VOC in 1955-70 showed a clear tendency to overrepresentation of rheumatic fever in the group with mitral lesions compared with the group with aortic lesions.

A. Year of death and its relation to rheumatic fever

An analysis of the deaths during the study period is given in Fig. 70.

In Hall's material the frequency of deaths was fairly constant throughout his study period (1954-74), and no correlation was found between the frequency and different degrees of certainty of the earlier rheumatic fever, suggesting that all the cases of rheumatic fever had been diagnosed and the mortality was therefore the same in the material. It did not appear that a higher degree of certainty of the diagnosis of rheumatic fever led to earlier death. As for the present material in which both the diagnosis of lesions and of the rheumatic fever were mostly included in the analysis, there was an increasing tendency in the 1960s, which was only natural since the material was not followed up so long after the time of diagnosis, and at that time all the patients were still alive. Generally speaking, the figures for the deaths of patients who were accepted in the study because of rheumatic fever were more constant than for those who were accepted because of cardiac lesions without preceding rheumatic fever. The accumulation of cases suggests that lesions shorten the expectancy of life, which is in agreement with what we found earlier regarding the duration of survival after the diagnosis of lesions.

B. Primary cause of death

Thanks to the high autopsy rate, it was possible to get a good survey of the causes of death in the various groups of the material.

Fig. 71 compares the Hall's material with ours. Hall's patients included a

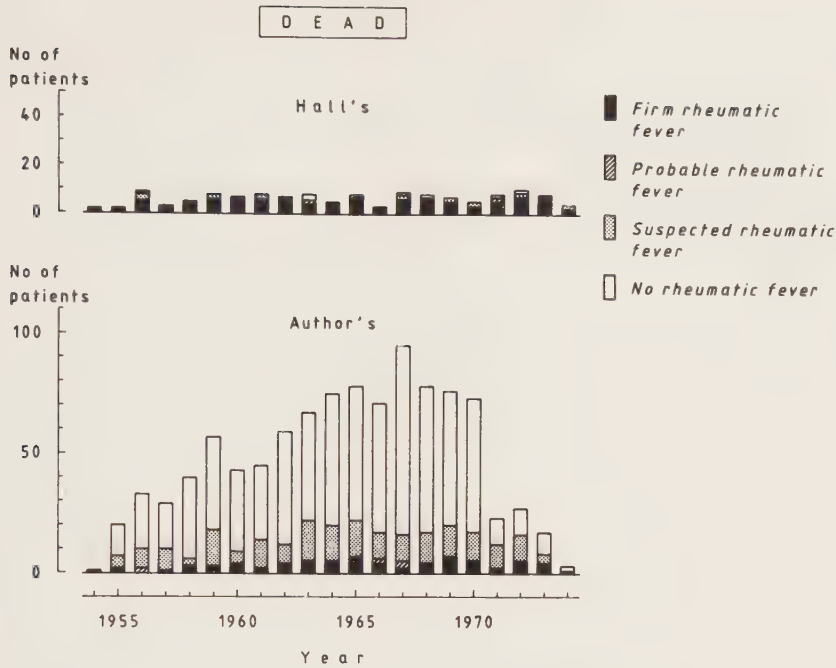


Fig. 70 Distribution of deaths among patients with signs of rheumatic heart disease.

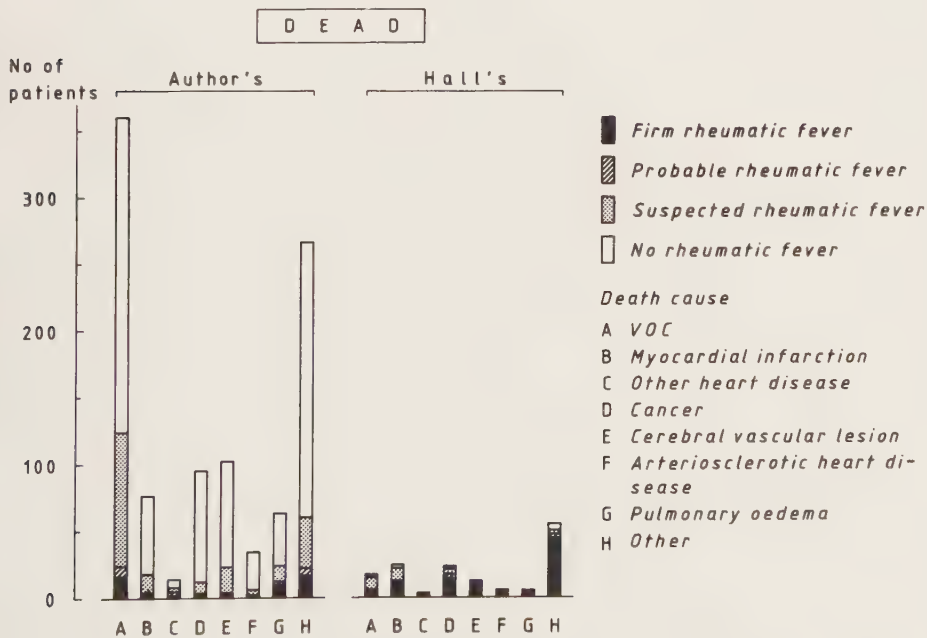


Fig. 71 Distribution of cause of death among patients with a diagnosis of rheumatic fever in their history.

small group who had heart lesions, but in whom the later analysis could not confirm previously assumed rheumatic fever, while the present material naturally contained a large number of patients who had entered the material because of heart lesions and had not had rheumatic fever.

The cause of death was judged from the pathologists' opinion of the primary and the contributory causes.

1. The present material

Of the patients who had with certainty had rheumatic fever, the lesion was primary cause of death in 17 (28.8 %), while the corresponding figure for those who probably or possibly had had rheumatic fever were 6 (33 %) and 101 (51.0 %), respectively. Conditions other than heart diseases and cancer were responsible for a large proportion of the deaths, but cancer claimed 4.3 %. Of the patients who had had rheumatic fever, myocardial infarction was not an uncommon cause of death (6.4 %) and cerebral vascular complications, as a rule due to embolism, was the primary cause in 8.3 %.

Other cardiac complications, ischaemic heart disease, decompensation, pulmonary oedema and other diseases of the heart were the primary causes in a considerable proportion of the material. The deaths from decompensation could probably be related to rheumatic lesions.

Among the patients who had not had rheumatic fever, the primary cause of death was cardiac lesion in 32.9 %, cancer in 11.1 % and embolism in 5.0 %.

2. Hall's material

In Hall's material of rheumatic fever covering the years 1930-54 the figures were naturally smaller and the figures for those with a firm diagnosis of rheumatic fever higher. In the group that had had rheumatic fever the frequency of deaths from heart lesions was lower than in the group with lesions without previous rheumatic fever. Here, too, the frequency of deaths from causes other than heart disease or cancer was substantial. The frequency of deaths from myocardial infarction was somewhat higher in the group that had had rheumatic fever. For patients who had had rheumatic fever the causes of death were valvular lesions in 11.9 %, cancer in 15.8 %, embolism in 3.1 % and myocardial infarction in 14.2 %.

Summing up, heart disease (lesion + infarction + other heart disease + ischaemic heart disease + decompensation) is the commonest cause of death in patients who have had rheumatic fever - in the present material it was responsible for 65.4 % of deaths and in Hall's material in 34.1 %. Cerebral catastrophes were in the present material responsible for 8.2 % of the deaths and in

Hall's 9.5 % suggesting that embolism due to the lesion is not a dominating cause of death.

Analysis of the pathologist's reports of those patients who had died from cardiac lesions showed that the frequency of a firm diagnosis of previous rheumatic fever was somewhat higher in Hall's material than in ours. Heart disease as the primary cause of death was also common in the group that had not had rheumatic fever but in which many of the patients died from conditions other than heart disease and cancer. Of the patients in the present material who had a history of rheumatic fever the main cause of death was valvular disease, followed in order of importance by pulmonary oedema, cerebral vascular catastrophe and myocardial infarction, while the mortality from cancer was low. In Hall's material other causes of death were predominant, such as cancer and myocardial infarction; and among patients who had lesions but no history of rheumatic fever, the dominating causes were the heart lesions, and conditions other than cerebral vascular catastrophe, cancer and myocardial infarction.

Among patients who had had rheumatic fever, heart lesions were the primary cause of death in only 33.4 %, and together with those patients who had died from pulmonary oedema it was 40.1 %. Of the patients who developed lesions not due to rheumatic fever, 32.1 % died from lesions and together with pulmonary oedema 37.5 %.

II. Lesions

A. Time factors

Interval between rheumatic fever and diagnosis of lesions

It is clear from Table VII that among the patients who had had rheumatic fever and died there was a successive accumulation of lesions with the interval after the diagnosis of rheumatic fever. Many patients in the present material had lesions within 5 years after rheumatic fever and this pattern was the same for every subsequent 5-year period.

Interval between diagnosis of lesion and death

In Hall's patients who were still alive at this re-examination and later died, the duration of survival was long, namely 19 years after the diagnosis of mitral lesions and 15 years after aortic lesions. In the present material the figures were substantially lower, viz 3.2 and 1.7 years, respectively. Hall's figures are probably more correct for the patients that had had rheumatic fever. Fig. 72 shows that in the material where the author's patients dominated, this striking overrepresentation of a short survival after the diagnosis of the lesions can presumably be explained by the fact that in many cases the lesions were not diagnosed before death. But in some cases the interval was much longer, namely up

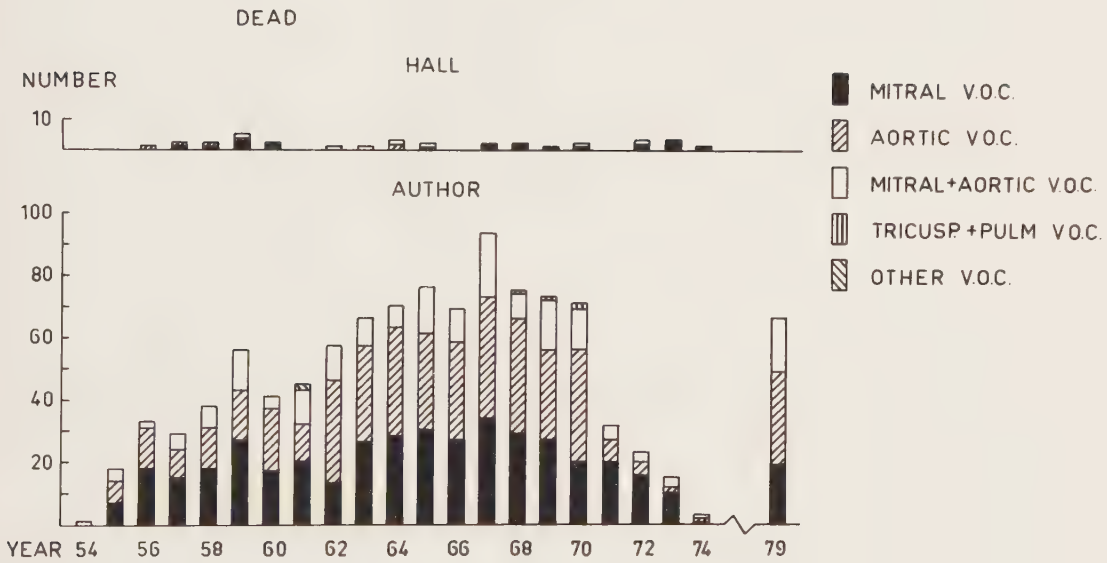


Fig. 73 Number of deaths among patients with V.O.C. diagnosed in the study period.

to 50 years for mitral lesions and up to 40 for aortic lesions.

B. Year of death

Most of the patients in the present material had cardiac damage and the values given in Fig. 73 agree well with the tendencies seen in rheumatic fever. Broadly speaking, the frequency of patients with lesions who had died increased somewhat during the study period and was highest in 1967. In the beginning of the study period mitral lesions were the more predominant cause of death, but towards the end of the period, aortic lesions, and also the frequency of double lesions showed a certain increase. This appeared to agree with the successive increase in the frequency of aortic lesions during the study period. The figures after 1970 refer to patients who had died before the review and are not representative.

To judge any possible tendency of a trend the number of patients who died in 1979 was also calculated in the same way. It was found that the number of deaths had persisted unchanged. In 1979, 19 patients died from pure mitral lesions, 30 from pure aortic and 17 from bivalvular lesions, i.e. totally 66 patients. This is roughly the same frequency as in 1970, although by 1979 Malmö had lost 30 000 inhabitants. VOC thus continued to be a serious medical problem.

C. Primary cause of death

Fig. 74 compares Hall's material with ours. In Hall's material about half of the deaths were due to a cardiac lesion, which should therefore be fairly representative of patients with a previous history of rheumatic fever and followed up until death from rheumatic lesions. In the present material, which includes patients with lesions with and without a history of rheumatic fever, the main cause of death in 35.7 % was the heart lesions. The next most common causes were conditions other than heart disease and cancer. Also myocardial infarction and cerebrovascular catastrophes were common causes, the latter probably due to embolism. The frequencies were 25.9 % for other causes, 9.9 % for cancer, 7.6 % for myocardial infarction, 5.8 % for decompensation and pulmonary oedema and 3.0 % for morbus arterioscleroticus and 10.1 % for cerebrovascular catastrophes. The frequency of deaths from heart lesion as the primary cause of death was highest for those who had had double valvular lesions.

Summing up, heart disease, including arteriosclerosis, infarction, heart failure and embolic complications, were the commonest causes of death in the material as a whole, while cancer was relatively uncommon.

D. Secondary cause of death

The VOC is reported as secondary cause of death in 26.8 % of the patients in the

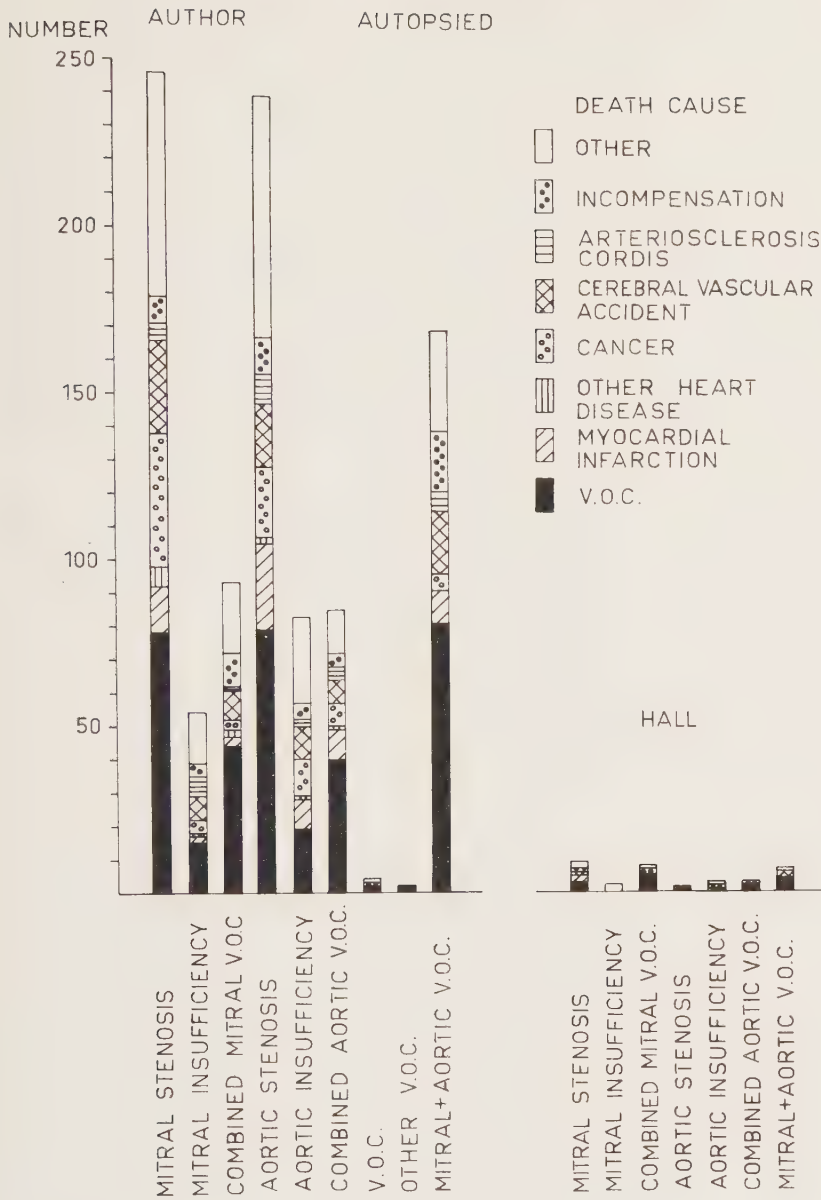


Fig. 74 Cause of death in autopsied patients.

present material and in 25 % in Hall's patients. Heart failure is also an important secondary cause of death in the VOC patients.

GENERAL SUMMARY

A. Short historic survey

Rheumatic fever has been well known since the 17th century and its association with rheumatic heart lesions, since 1778.

Chorea has been known since the 18th century; and surgical methods for the treatment of rheumatic heart lesions appeared in 1948. In the present century all epidemiologic studies have shown a decline in the frequency of rheumatic fever and often also rheumatic heart lesions. We have tried to describe the situation and the development in a well-to-do country like Sweden.

B. Material and methods in this study

Malmö is the third largest town in Sweden. During the study period (1930 to 1970) its population increased from 131 249 inhabitants to 265 505. It has only one hospital (Malmö general hospital), which takes care of all patients requiring hospitalization as well as the majority of ambulatory patients. This means that all information on the patients is collected and treated in a uniform way.

Our investigation consisted of two series of patients, namely those included in Hall's study of rheumatic fever (1930-54) and the present material (1955-70), consisting of all patients who had had rheumatic fever or a new diagnosis of rheumatic valvular disease in 1955-70. Our patients were compared with Hall's former group with valvular damage, but his cases were not reviewed by us because the valvular lesions in the latter had already been diagnosed and analysed in Hall's study. The records of a wide variety of diagnoses were scrutinized to trace all patients who had had rheumatic fever and rheumatic valvular disease. The autopsy frequency in Malmö is remarkably high - almost 90 % - and the statistical analysis of the causes of death was therefore reliable.

The review of our patients included a questionnaire, analysis of their hospital records, physical examination, certain laboratory studies, ECG, roentgen examination and serological tests. In certain groups the review comprised examination regarding digitalis treatment, lung function, further physiological tests, examination for rheumatoid arthritis and questions concerning ornithosis.

To get a material as comparable as possible to Hall's we used the same modification of Jones' criteria as Hall in spite of the fact that certain minor changes have since been made in the classification of rheumatic fever.

We also used the same criteria as Hall in the classification of valvular lesions, namely NYHA:s criteria from 1955.

The purpose of the investigation was to elucidate the natural history of

rheumatic fever and rheumatic valvular disease during a long period in a European country with a high socio-economic standard. Changes occurring between 1930 and 1970 have due to the selection of the material in Malmö been possible to study very closely.

C. Rheumatic fever

Number

During the study period the population almost doubled, yet the absolute number of cases of rheumatic fever substantially fell, except in association with the second world war, when it showed a relative increase, probably due to poorer socio-economic conditions at that time. Obviously the diagnosis of rheumatic fever could be established with a higher degree of certainty in those alive and after-examined than in those who had died and in whom the diagnosis was checked only on the basis of data obtainable from their hospital records.

Criteria

The criteria for a diagnosis of rheumatic fever were, in decreasing order of frequency: polyarthrititis, fever, increased ESR, evidence of previous earlier streptococcal infection. Most of the patients met these requirements and allowed a firm diagnosis in 729, a probable diagnosis in 91 and a suspect diagnosis in 325. The sex distribution showed a slight overrepresentation of females and the average age was about 22 years. Nephritis was not uncommon and was found most often in the group that did not later in life develop valvular lesions possibly suggesting that nephritogenic streptococcal strains rarely lead to endocarditis.

Findings of interest made at the interviews were that rheumatoid arthritis, erythema nodosum and "growing pains" were common.

Age

The age at onset of rheumatic fever ranged from 5 to 30 years. The corresponding figures for endocarditis and chorea were respectively 5-20 and 10 years. A PR-time of more than 0.21 was found in only 18 of 220 patients with endocarditis. Of the 95 patients with chorea only 54 had had rheumatic fever.

Ornithosis

Ornithosis as a cause of rheumatic fever can be dismissed since only one of our patients with valvular disease had had the condition, and the frequency of contact with birds was largely equal among those with and without valvular disease and was also equal to that in a normal population.

Serology

In the material as a whole there was a tendency to a somewhat elevated AST-titre, which can hardly have had anything to do with earlier rheumatic fever, but possibly to a low resistance to infections with streptococci.

A positive Waaler-Rose test was found with a frequency definitely not below normal. And the frequency of a positive acryl fixation test was slightly higher than that expected in a normal population, while that of rheumatoid arthritis was not.

Social factors

Rheumatic fever, and to some extent also valvular disease, were much more common in poor areas of the town. To belong to a low social class implies a greater risk of rheumatic fever, especially if also the parents belonged to the same class, so-called social heritage.

D. Rheumatic valvular lesion

Interval

The frequency of valvular lesions increases with the interval after rheumatic fever. After 10-15 years it was, on the average 5 %, and after 30-35 years it was 10 %. This successive increase makes it difficult to calculate a mean interval between rheumatic fever and the development of valvular disease in patients who have not been regularly followed-up until death. The mitral valves were involved almost twice as often as the aortic valves. The frequency of known rheumatic fever among the patients reviewed was higher than that among those autopsied probably due to the difference in available anamnestic data. In patients who had had rheumatic fever the lesions appeared between the ages 50-75, most often between 60 and 65. The corresponding figures for those who had not had rheumatic fever were higher, i.e. 55-70 and 65-70 respectively. The patients with combined lesions in either the mitral or the aortic valve had rheumatic fever much earlier in life than those with stenosis or insufficiency. Chorea was rare, and when it occurred it was usually in patients with mitral valvular lesions.

Penicillin

Treatment with penicillin for tonsillitis did not appear to reduce the frequency of lesions. Tonsillitis was not always treated with penicillin in our material. In patients treated with cortisone at the time of the rheumatic fever the frequency of valvular disease was somewhat lower than among those who were not.

Incapacity to work

This was common among the patients who had had rheumatic fever, but most of them could manage their daily life with only little or no medical help. The median age in the group at the review was: for the men 51.6 and for the women 54.

Frequencies

The total number of patients with heart lesions has not changed to any noteworthy extent, but the proportion of the population with mitral lesions has decreased and the proportion with aortic lesions has increased (Fig. 75). The decrease is not proportional to that of rheumatic fever. One might, thus, assume that mitral lesions are preponderantly of rheumatic nature, while aortic lesions are largely not i.e. not due to streptococcal infection.

Among those who had had rheumatic fever the sequelae were clearly dominated by combined mitral lesions and mainly mitral stenosis, while in those who had not had rheumatic fever there was an overrepresentation of aortic stenosis. On the average 200-250 new cases of rheumatic lesions were diagnosed per 5-year period. In the 60s the figures were somewhat higher, about 370 per 5-year period, which is remarkable in the light of the decreasing frequency of rheumatic fever even if the number of inhabitants had risen. This may be due to lesions among the high percentage of patients with rheumatic fever during and after the second world war. A control of the frequency of autopsied VOC patients 1978 also confirms the relative stability in lesion rates. Most of the patients with lesions had died and were studied on the basis of information available from the autopsy reports. The frequency of deaths from aortic lesions in that group was higher than that among patients with mitral lesions and double lesions. Lesions were diagnosed with increasing frequency up to the age of 55, but sometimes after this age. Only 30.2 % of the patients with lesions were men. Those with mitral lesions had had rheumatic fever at the age of 19-20 years; those with aortic lesions, at 22-28 years. Of those patients who had had endocarditis, the rheumatic fever in Hall's material had occurred in one patient at 12 years and led to aortic lesions, while in the present material the onset had occurred, on the average, at 44 years of age and mostly resulted in mitral lesions. The onset of chorea leading to mitral lesions occurred, on an average, at 10-11 years of age. In Hall's material lesions were diagnosed at, on an average, 38 years of age; in the present material, at 49.

Age

The frequency of demonstrated lesions increased successively from 5-10 year age to reach a maximum at 50-55 years. The onset of heart failure was most common

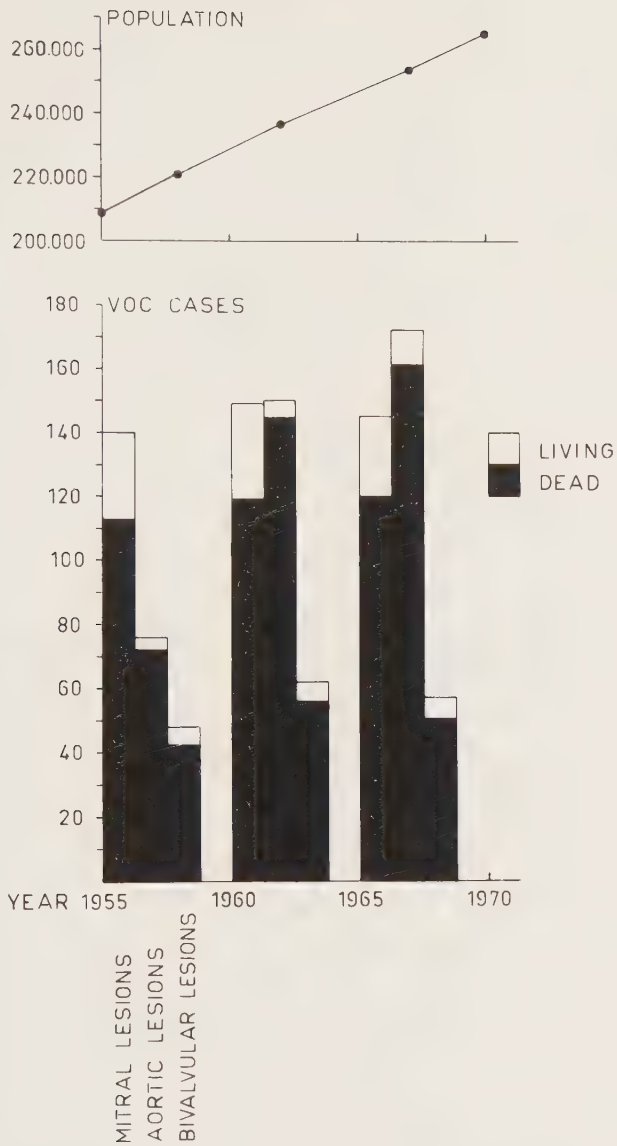


Fig. 75 Number of new diagnoses of heart lesions in 1955-70 and the development of the population.

between the ages of 45 and 50, but was always lower than that of valvular lesions. The youngest patients admitted for heart surgery were between 25 and 30 years of age, but surgery was most common between the age of 40-50. It was not done on patients above 60 years. Operations were performed 5-30 years after the onset of the lesions. None were operated upon within 5 years of the diagnosis of the lesions. Patients with mitral lesions died, on the average, at 60 years of age; those with aortic lesions and double lesions, earlier.

Symptoms

Heart symptoms began soon after the diagnosis of the lesions, and in the present material this was the rule. For aortic lesions the ages were 40 and 50 years, respectively.

Complications

The frequency of cerebrovascular lesions was low. Subacute bacterial endocarditis was diagnosed in only 3 patients. Heart failure began, on the average, 6 years after the onset of the lesion, but mitral insufficiency and aortic stenosis produced strikingly late symptoms of decompensation. Among patients with mitral lesions and impaired working capacity the interval between the diagnosis of the lesion and impairment of working capacity was, on the average, 8 years. The figures were the same for aortic lesions. One hundred and thirty patients had been granted a sick-pension. In most of the patients pregnancy and reproduction did not seem to be contraindicated. When failure of the left half of the heart occurred, it usually did so after 8 years; failure of the right half, earlier. Arrhythmia occurred after about 7 years. About 15 % of such patients had had one or more cerebrovascular attacks after about 7 years. Hypertension appeared late, on the average, after about 11 years. The blood pressures were, however, strikingly often normal. Cerebrovascular lesions occurred in patients as young as 30-35 years of age.

Surgical treatment

Cardiac surgery was done on patients between the ages of 40 and 54, while pace-makers were implanted only rarely, and then only in old patients.

When surgery was performed, it was usually about 4 years after the diagnosis of the lesion - somewhat longer in patients with combined lesions.

Digitalis

The digitalis concentration in our material was mostly lower than that regarded as the therapeutic range. The study shows a depressing experience of the inherent

difficulties in giving a heart population in even relatively younger ages adequate digitalis treatment.

Anemia

On determination of the haptoglobin level as a test for hemolysis, the values found were low in patients with valvular prosthesis, and also lower in those with unoperated aortic lesions than in those with both mitral and aortic lesions.

Rheumatoid arthritis

The frequency of rheumatoid arthritis was somewhat higher than expected.

Spirometry

Spirometry showed a moderate decrease in vital capacity and increased residual volume and some reduction of FEV_1 . Smoking had a negative effect on the spirometric findings.

Roentgen

As a rule, patients with mitral stenosis showed X-ray changes. They were also common in patients with other types of mitral damage. Also patients with aortic and double lesions showed clear X-ray changes. One third of the patients with aortic as well as mitral lesions showed calcifications in the valves. But some patients without diagnosed valvular lesions showed calcifications in the valves, namely in 8 in the mitral and in 20 in the aortic valves, for which reason the diagnostic value of cineradiography in the diagnosis of lesions may be questioned, even though it showed a higher frequency of calcifications in the lesion patients.

E. Patients who had died

In the group of patients the percentage of those who had had rheumatic fever was higher among those who had had mitral lesions than among those who had had aortic lesions. But the percentage of rheumatic fever was low owing partly to the fact that it had not been possible to interview them. Of those who had rheumatic fever and died from the cardiac lesions, 28.8 % of the deaths were in those who had firm rheumatic fever, 33.3 % in those in whom the diagnosis was probable and 51.0 % in those in whom the diagnosis was suspect, i.e. in 33.4 % of all the patients who had died. If those who died from pulmonary oedema be added the figure would be 40.1 % studied in the present material. Valvular damage was the cause of death in 9 % of Hall's material. In the present study the diagnosis of lesions was often made during or in close relation to autopsy. The duration of survival in Hall's material was 19 years after the diagnosis of mitral damage

and 15 years after the diagnosis of aortic damage. The number of cases of patients who had died from valvular lesions increased during the latter part of the investigation and was highest in 1967. In Hall's material the valvular lesions were the cause of half of the deaths; in the present material, 35.7 %. The next most common causes were cancer and thereafter other forms of heart disease. It should be added that 26.8 % of the patients in the present material with lesions had valvular lesions noted as a contributory cause of death. The corresponding figure in Hall's material was 25 %. The valvular lesions were therefore the commonest causes of death among patients with this diagnosis. Stenosis was the commonest form of mitral damage in the patients examined post mortem.

F. Concluding remarks

The frequency of rheumatic fever has markedly decreased and the age at onset has increased.

The natural history of cardiac lesions has not changed to any noteworthy extent. But the total number of patients with mitral lesions and of patients with rheumatic fever in their history has decreased, while the number of aortic lesions has increased as has that of patients without any known previous attack of rheumatic fever. Mitral lesions seem to be of rheumatic nature more often than aortic lesions. The factors responsible for the decrease in the frequency of rheumatic fever seem to be mainly of socio-economic nature.

However, the improved socio-economic conditions do not seem to have appreciably changed the clinical picture of rheumatic heart disease.

The heart status in a population of patients with cardiac lesions is described and apart from the level of digitalis in the blood, they appear to be adequately treated.

The investigation did not produce any convincing evidence that treatment of rheumatic fever with penicillin has any effect on the development of rheumatic heart lesions.

ACKNOWLEDGEMENTS

I am very much indebted to:

Docent Bengt W Johansson, for never-failing interest and help in every respect throughout the investigation;

Professor Bertil Hood, for inspiration and constructive criticism;

Professor Jan Waldenström, for advice and for interest shown in the investigation;

Mrs Lillemor Welam, for never-tiring, skilful secretarial help and angelic patience throughout the whole investigation;

Docent Peter Aspelin, for help with the roentgenological studies;

Fil kand Hasse Kvist, for data programming and statistical help;

Docent Paul Hall, whose earlier work inspired me throughout the investigation;

Professor Sten Winblad, for interest in the serological part of the study and help with immunological analyses;

Professor Sven-Eric Lindell, for help with the lung function studies;

Professor Carl-Bertil Laurell, for chemical analyses;

Mrs Ann-Mari Pauler, for help with the patients' records in the beginning of the study;

Mrs Inger Ericsson and Mrs Eva Willner, for skilful help with examination of the patients;

Mrs Gunvor Nilsson and Mr Lars Jansson, for drawing the diagrams;

My colleagues, Jörgen Malmquist and Frank Wollheim, for fruitful discussions;

The heads of the medical departments of Serafimerlasarettet, Stockholm, Sahlgrenska sjukhuset, Gothenburg, Helsingborg, Hässleholm, Kristianstad, Lund, Örup, Trelleborg, Ystad and Ängelholm, for help with examination of the patients.

This work was supported by grants from The Swedish National Association against Heart and Chest Diseases, Hulda Almroth's foundation, H.G. Murath's foundation, Greta and Johan Kock's foundation, Ernhold Lundström's foundation, Malmö Sjukvårdsstyrelse, Svenska Livförsäkringsbolags nämnd för medicinsk forskning, and Alfred Österlund's foundation.

REFERENCES

1. Åberg, H. & Cullhed, I.: Direct current conversion of atrial fibrillation - long-term results. *Acta Med Scand* 184:433, 1968.
2. Acheson, M.M.: The epidemiology of acute rheumatic fever 1950-64. *J Chron Dis* 18:723, 1965.
3. Adams, G.F., Merrett, J.D., Hutchinson, W.M. & Pollock, A.M.: Cerebral embolism and mitral stenosis: survival with and without anticoagulants. *J Neurol Neurosurg Psychiatry* 37:378, 1974.
4. Allander, E.: A population survey of rheumatoid arthritis. *Acta Rheum Scand (Suppl)* Uppsala 1970.
5. American Heart Association, 1955, see Jones' criteria (modified).
6. American Heart Association, 1956, see Jones' criteria (revised).
7. American Rheumatism Association, 1956, see Ropes et al.
8. American Rheumatism Association, 1958, see Ropes et al.
9. Anderson, H.C. & McCarty, M.: Determination of C-reactive protein in the blood as a measure of the activity of the disease process in acute rheumatic fever. *Am J Med* 8:445, 1950.
10. Anonym: Cardiac mortality and socio-economic status. *Stat Bull Metropol Life Ins Co* 48:9, 1967.
11. Anonym: Is rheumatic fever necessary? *JAMA* 214:361, 1970.
12. Anonym: Course and prophylaxis of rheumatic fever. *N Engl J Med* 285:1205, 1971.
13. Anonym: Etiology of acquired valvar heart disease. *Lancet* 1:899, 1971.
14. Anonym: Rheumatic fever control. *JAMA* 226:190, 1973.
15. Anschütz, F. & Wippenfürth, U.: Über die Abnahme und das zunehmende Alter von rheumatischen Herzklappenfehlern. *Z Kreislaufforsch* 61:305, 1972.
16. Aron, A.M., Freeman, J & Carter, S.: The natural history of Sydenham's chorea. *Am J Med* 38:83, 1965.
17. Askey, K.M. & Bernstein, S.: The management of rheumatic heart disease in relation to systemic arterial embolism. *Prog Cardiovasc Dig* 3:220, 1960.
18. Ayoub, E.M.: Streptococcal infections and their sequelae. In: *Clinical concepts of infectious diseases* (ed. L.E. Cluff and J.E. Johnsson), pp. 215-229. Williams and Wilkins, Baltimore 1972.
19. Ayoub, E.M. & Wannamaker, L.W.: Evaluation of the streptococcal DNase and DNPase antibody tests in acute rheumatic fever and acute glomerulonephritis. *Pediatr* 29:527, 1962.
20. Ayoub, E.M. & Wannamaker, L.W.: Streptococcal antibody titers in Sydenham's chorea. *Pediatr* 38:946, 1966.

21. Baggenstoss, A.H. & Titus, J.L.: Rheumatic and collagen disorders of the heart. In: Pathology of the heart and blood vessels (ed. S.E. Gould), pp. 649-680. Third edition, 1968.
22. Bailey, G.W., Braniff, B.A., Hancoek, E.W. & Cohn, K.D.: Relation of left atrial pathology to atrial fibrillation in mitral valvular disease. *Ann Intern Med* 69:13, 1968.
23. Ballonius, G. (Guillaume De Baillou): Cited by Wilson, M.G., 1940.
24. Barlow, T. & Warner, F.: Cited by Wilson, M.G., 1940.
25. Barnert, A.L., Terry, E.E. & Persellin, R.H.: Acute rheumatic fever in adults. *JAMA* 232:925, 1975.
26. Begbie, J.: Cited by Jacobsson, E. *Acta Paediatr Scand* (Suppl) 63, 1946.
27. Behrend, T., Lawrence, J.S., Behrend, H. & Koch, R.: Eine longtudinale Studie im Hinblick auf rheumatische Erkrankungen in der ländlichen Bevölkerung von Oberhörlen in Hessen. *Z Rheumaforsch* 31:153, 1972.
28. Bell, H., Pugh, D. & Dunn, M.: Failure of cardioversion in mitral valve disease. *Arch Intern Med* 119:257, 1967.
29. Berk, J.E. & Canete, D.: Penicillin prophylaxis in rheumatic fever prevention. *Jpn Circ J* 39:196, 1975.
30. Besterman, E.: The changing face of acute rheumatic fever. *Br Heart J* 32:579, 1970.
31. Bhattacharya, S.K., Jha, B.N. & Somani, O.N.: Carditis in acute rheumatic fever in Varanasi, India. *Trop Geogr Med* 26:271, 1974.
32. Bing, G.T.: Cardiovascular disease in Djakarta, Indonesia. *Trop Geogr Med* 22:289, 1970.
33. Bisno, A.L., Pearce, I.A., Wall, H.P., Moody, M.D. & Stollerman, G.H.: Contrasting epidemiology of acute rheumatic fever and acute glomerulonephritis. *N Engl J Med* 283:561, 1970.
34. Biörck, G., Winblad, S. & Wulff, H.: Studies in mitral stenosis. II. Observations on incidence of active rheumatic carditis in left auricular appendages resected at operation for mitral stenosis. *Am Heart J* 44:325, 1952.
35. Biörck, G., Axén, O., Wulff, H., Lundskog, O., Krook, H. & Bülow, K.: Studies in mitral stenosis V. Evaluation of immediate and late results on fifty patients, operated upon since 1950. *Acta Med Scand* 151:19, 1955.
36. Björk, V.O., Henze, A. & Carlström, A.: Haematological evaluation of the Björk-Shiley tilting-disc valve prosthesis in isolated aortic valvular disease. *Scand J Thorac Cardiovasc Surg* 8:12, 1974.
37. Björk, V.O., Henze, A. & Holmgren, A.: Five years. Experience with the Björk-Shiley tilting-disc valve. *J Thorac Cardiovasc Surg* 68:393, 1974.
38. Björk, V.O., Henze, A. & Holmgren, A.: Long-term results with the Björk-Shiley tilting-disc valve in aortic valvular disease. *Isr J Med Sci* 11:161, 1975.

39. Bland, E.F. & Duckett Jones, T.: Rheumatic fever and rheumatic heart disease. *Circulation* 4:836, 1951.
40. Bläker, F.: Tonsille und Immunologie. Nordwestdeutschen HND-Kongress Hamburg 23:265, 1975.
41. Bock, K.: Die Änderung der Herztätigkeit im Verlauf der rheumatischen Karditis im Kindesalter. *Dtsch Med Wochenschr* 87:2013, 1962.
42. Bonchek, L.I. & Starr, A.: Late results of mitral and aortic valve replacement. *Isr J Med Sci* 11:152, 1975.
43. Bonchek, L.I. & Starr, A.: Ball Valve Prostheses: Current appraisal of late results. *Am J Cardiol* 35:843, 1975.
44. Bonfiglio, T. & Atwater, E.C.: Heart disease in patients with seropositive rheumatoid arthritis. *Arch Intern Med* 124:714, 1969.
45. Borsche, A.: Das rheumatische Fieber im Kindesalter. *ZFA* 47:218, 1971.
46. Bouillaud, J.B.: *Traité clinique du rhumatisme articulaire, et de la loi coincidence des inflammations du coeur avec cette maladie.* J.B. Baillière, Paris, 1840.
47. Bright, R.: Cited by Wilson, M.G., 1940.
48. Brodeur, M.T., Sutherland, D.W., Koler, R.D., Starr, A., Kimsey, J.A. & Griswold, H.E.: Red blood survival in patients with aortic valvular disease and ball-valve prosthesis. *Circulation* 32:570, 1965.
49. Brown, J.W., Myerowitz, P.D., Cann, M.S., Colvin, S.B., McIntosh, C.L. & Morrow, A.G.: Clinical and hemodynamic comparisons of Kay-Shiley, Starr-Edwards No. 6520, and Reis-Hancock porcine xenograft mitral valves. *Surgery* 76:983, 1974.
50. Brownell, K. & Bailen-Rose, F.: Acute rheumatic fever in children. *JAMA* 124:1593, 1973.
51. Burch, G.E. & Giles, T.D.: The role of viruses in the production of heart disease. *Am J Cardiol* 29:231, 1972.
52. Burch, G.E., Giles, T.D. & Colcolough, H.L.: Pathogenesis of "rheumatic" heart disease: critiques and theory. *Am Heart J* 80:556, 1970.
53. Burch, G.E., Sun, S.C., Colcolough, H.L., Sohal, R.S. & DePasquale, N.P.: Coxsackie B viral myocarditis and valvulitis identified in routine autopsy specimens by immunofluorescent techniques. *Am Heart J* 74:13, 1967.
54. Burch, G.E., DePasquale, N.P., Sun, S.C., Hale, A.R. & Mogabgab, W.J.: Experimental coxsackievirus endocarditis. *JAMA* 196:137, 1966.
55. Burda, C.D. & Sanders, C.V.: Chronic post-rheumatic-fever (Jaccoud's) arthritis. *Arch Intern Med* 120:712, 1967.
56. Burgio, G.R. & Vaccaro, R.: Immunologische Befunde bei rheumatischen Erkrankungen im Kindesalter. *Monatsschr Kinderheilkd* 117:553, 1969.

57. Burgio, G.R. & Vaccaro, R.: Immunological remarks on rheumatic fever in children with reference to heart-reactive serum factors, immunoglobulins and Beta_{1C} - globulin levels. *Helv Paediatr Acta* 27:315, 1972.
58. Butler, V.P. & Chen, J.P.: Digoxin-specific antibodies. *Proc Natl Acad Sci USA* 57:71, 1967.
59. Bywaters, E.G.: Current concepts concerning the pathogenesis of rheumatism. *Trans Med Soc Lond* 89:248, 1973.
60. Böttiger, L.D.: Hög SR utan känd orsak! Vad göra? I: Medicinsk årsbok, 69-73, 1975.
61. Carpenter, D.F., Golden, A. & Roberts, W.C.: Quadrivalvular rheumatoid heart disease associated with left bundle branch block. *Am J Med* 43:922, 1967.
62. Carvalhal, S.S., Atrá, E., Saad, F.A. & Pupo, R.A.: Pneumopathie rhumatismale. *Rev Rhum* 36:597, 1969.
63. Cavelti, P.A.: Autoantibodies in rheumatic fever. *Proc Soc Exp Biol Med* 60:379, 1945.
64. Chen, S.T., Dugdale, A.E. & Puthuchery, S.D.: Beta hemolytic streptococcal carriers among normal school-children. *Trop Geogr Med* 24:257, 1972.
65. Cheng, C-T. & Persellin, R.H.: Interference by Clq in slide latex tests for rheumatoid factor. *Ann Intern Med* 75:683, 1971.
66. Chesley, L.C.: Rheumatic cardiac disease and pregnancy: Long-follow up of women with severe cardiac impairment. *Obstet Gynecol* 29:560, 1967.
67. Chesley, L.C.: The remote prognosis for pregnant women with rheumatic cardiac disease. *Am J Obstet Gynecol* 100:732, 1968.
68. Chesley, L.C.: Rheumatic cardiac disease in pregnancy. *Obstet Gynecol* 46:699, 1975.
69. Christian, C.L.: Eighteenth rheumatism review. Review of American and English Literature for the years 1965 and 1966. *Arthritis Rheum (Suppl)* 5:23, 1968.
70. Coburn, A.F. & Cone, L.A.: The natural history of rheumatic fever, incurable, fatal pancarditis: Forty years later. *Am J Dis Child* 111:115, 1966.
71. Cohn, L.H., Lambert, J.J., Castaneda, A.R. & Collins Jr, J.J.: Cardiac valve replacement with the stabilized glutaraldehyde porcine aortic valve: Indications, operative results, and follow-up. *Chest* 68:162, 1975.
72. Cosh, J.A.: The heart and the rheumatic diseases. *Rheum Phys Med* 11:267, 1972.
73. Cossermelli, E.M. & Pastor, E.M.: Estudio critico de los grandes criterios en el diagnostico de la fiebre rheumatica. *Arq Bras Cardiol* 28:46, 1975.
74. Coste, F., Delbarre, F., Frézal, J. & Peltier, A.: Facteurs Génétiques des rhumatismes inflammatoires et des connectivites. *Rev Rhum* 33:378, 1966.
75. Coulshed, N., Epstein, E.J., McKendrick, C.S., Galloway, R.W. & Walker, E.: Systemic embolism in mitral valve disease. *Br Heart J* 32:26, 1970.

76. Crawford, M.J.: An increase in rheumatic fever. *Lancet* 2:842, 1973.
77. Criteria committee, New York Heart Association: Physical capacity with heart disease. In: *Diseases of the heart and blood vessels: Nomenclature and criteria for diagnosis*, p. 114. Boston 1964.
78. Cuddigan, B.J. & Speller, D.C.: Fragmentation anaemia in a case of aortic valve disease. *Guy's Hospital Reports* 122:169, 1973.
79. Cullhed, I.: Aortic stenosis. *Almqvist & Wiksell* 1964.
80. Cumming, G.R.: Acute rheumatic fever. *Can Med Assoc J* 111:819, 1974.
81. Cuppari, G., Quagliata, F., Ieri, A. & Taranta, A.: Lymphocyte transformation with streptolysin 5 preparations and inhibition of streptolysin 5 by serum in rheumatic fever and other rheumatic diseases. *J Lab Clin Med* 80:165, 1972.
82. Daikos, G. & Weinstein, L.: Streptococcal bacteriostatic antibody in patients treated with penicillin. *Proc Soc Exp Biol Med* 78:160, 1951.
83. Davis, E.: Criteria of rheumatic fever. *Lancet* 1:1043, 1970.
84. Denny, F.W.: Prevention of rheumatic fever. *Circulation* 43:983, 1971.
85. Duckett Jones, T.: The diagnosis of rheumatic fever. *JAMA* 126:481, 1944.
86. Dunlap, M.B. & Bergin, J.W.: Subsequent health of former carriers of hemolytic streptococci. *NY State J Med* 73:1875, 1973.
87. Dönhardt, A., Mai, K. & Prinz, H.: Probleme der antibiotischen und antibakteriellen Langzeittherapie in der inneren Medizin. *Z Gesamte Inn Med* 8:83, 1972.
88. Ebert, P.A.: Surgical treatment of congenital and acquired valvular heart disease. *DM* 1, 1975.
89. Editorial: The decline of acute rheumatism. *Lancet* 1:32, 1957.
90. Editorial: Rheumatic fever. *Arthritis Rheum* 13:461, 1970.
91. Edström, G.: Febris rheumaticas klinik, profylax och terapi. *Finlands läkartidning* 8, 1953.
92. Edström, G.: Profylax mot reumatisk feber. *Svenska Läkartidningen* 50:1565, 1953.
93. Edström, G. & Gedda, P.P.: Investigation on the localisations and forms of some visceral anatomical lesions in rheumatic fever. *Acta Med Scand* 147:367, 1953.
94. Edwards, J.E.: On the etiology of calcific aortic stenosis. *Circulation* 26:817, 1962.
95. Ekelund, H., Enocksson, E., Michaëlsson, M. & Voss, H.: The incidence of acute rheumatic fever in Swedish children 1952-1961. *Acta Med Scand* 181:89, 1967.

96. Eliot, R.S.: The adult forms of heart disease often confused with rheumatic endocarditis. *RadioI Clin North Amer* 6:399, 1968.
97. Engleman, E.P., Hollister, L.E. & Kolb, F.O.: Sequelae of rheumatic fever in men. *JAMA* 155:1134, 1954.
98. Enticknap, J.B.: Biopsy of the left auricle in mitral stenosis. *Br Heart J* 15:37, 1953.
99. Ertugrul, A., Renda, Y., Saraciar, M., Oner, M. & Akay, S.: Electroencephalographic study in acute rheumatic carditis. *Am Heart J* 91:163, 1976.
100. Escudero, J., Skromne, D., Acolzin, C., Wabi, C. & Palacios Macedo, X.: Evolucion a largo plazo de 100 cardiopatas reumaticos rechazados para cirugia. *Arch Inst Cardiol Mex* 43:293, 1973.
101. Falk, J.A., Fleischman, J.L., Zabriskie, J.B. & Falk, R.E.: A study of HL-A antigen phenotype in rheumatic fever and rheumatic heart disease patients. *Tissue Antigens* 3:173, 1973.
102. Feinstein, A.R.: The natural histories of acute rheumatic fever. *Bull Rheum Dis* 17:423, 1966.
103. Feinstein, A.R. & Di Massa, R.: The prognosis significance of valvular involvement in acute rheumatic fever. *N Engl J Med* 260:1001, 1959.
104. Feinstein, A.R. & Spagnuolo, M.: The duration of activity in acute rheumatic fever. *JAMA* 175:83, 1961.
105. Feinstein, A.R., Spagnuolo, M., Jonas, S., Kloth, H., Tursky, E. & Levitt, M.: Prophylaxis of recurrent rheumatic fever. *JAMA* 206:565, 1968.
106. Feinstein, A.R., Spagnuolo, M., Jonas, S., Levitt, M. & Tursky, E.: Discontinuation of antistreptococcal prophylaxis. *JAMA* 197:949, 1966.
107. Feinstein, A.R., Spagnuolo, M., Wood, H., Taranta, A., Tursky, E. & Kleinberg, E.: Clinical characteristics of infections and recurrences. *Ann Intern Med (Suppl)* 60:68, 1964.
108. Feinstein, A.R., Stern, E.K. & Spagnuolo, M.: The prognosis of acute rheumatic fever. *Am Heart J* 68:817, 1964.
109. Feinstein, A.R., Taranta, A. & Di Massa, R.: Errors in the diagnosis of acute rheumatic fever. *NY State J Med* 60:2835, 1960.
110. Feinstein, A.R., Wood, H.F., Spagnuolo, M., Taranta, A., Jonas, S., Kleinberg, E. & Tursky, E.: Rheumatic fever in children and adolescents. *Ann Intern Med (Suppl)* 60:87, 1964.
111. Ferencz, C.: Rheumatic fever. *NY State J Med* 68:2025, 1968.
112. Finchum, R.: Rehabilitation following cardiac surgery. *Circulation (Suppl)* 43:151, 1971.
113. Findlay, I.I. & Fowler, R.A.: The changing pattern of rheumatic fever in childhood. *Can Med Assoc J* 94:1027, 1966.

114. Fleischhans, B., Holeckova, R. & Slamova, J.: The outcome of patients with rheumatic fever 30 years ago and today. *Vnitr Lek* 15:864, 1969.
115. Fleming, H.A. & Bailey, S.M.: Mitral valve disease, systemic embolism and anticoagulants. *Postgrad Med J* 47:599, 1971.
116. Fox, E.N., Pachman, L.M., Wittner, M.K. & Dorfman, A.: Primary immunization of infants and children with group A streptococcal M protein. *J Infect Dis* 120:603, 1969.
117. Freundlich, I.M.: Endocardial calcification. *CRC Crit Rev Diagn Imaging* 6:171, 1975.
118. Gadboys, H.L., Litwak, R.S., Niemetz, J. & Wisch, N.: Role of anticoagulants in preventing embolization from prosthetic heart valves. *JAMA* 202:134, 1967.
119. García-Palmieri, M.R.: Rheumatic fever and rheumatic heart disease as seen in the tropics. *Am Heart J* 64:577, 1962.
120. Gavrin, J.B., Tursky, E., Albam, R. & Feinstein, A.R.: Rheumatic fever in children and adolescents. *Ann Intern Med* 60:18, 1964.
121. Gersony, W.M., Willerson, W.D., Johnson, A.F. & Webb, W.R.: Aortic valvuloplasty during acute rheumatic fever. *J Thorac Cardiovasc Surg* 55:598, 1968.
122. Gharib, R.: Acute rheumatic fever in Shiraz, Iran. *Am J Dis Child* 118:699, 1969.
123. Ginsburg, I.: Mechanisms of cell and tissue injury induced by group A streptococci: Relation to post-streptococcal sequelae. *J Infect Dis* 126:294, 1972.
124. Glover, J.A.: Incidence of rheumatic diseases. *Lancet* 1:499, 1930.
125. Glover, J.A.: War-time decline of acute rheumatism. *Lancet* 2:51, 1943.
126. Glover, R.P., Bailey, C.O. & O'Neill, Th.J.: Surgery of stenotic valvular disease of the heart. *JAMA* 144:1049, 1950.
127. Goldstein, I., Halpern, B. & Robert, L.: Immunological relationship between streptococcus A polysaccharide and the structural glycoproteins of heart valve. *Nature* 213:44, 1967.
128. Gonzalez-Lavin, L. & Ross, D.N.: Autologous fascia lata valves in combined aortic and mitral valve replacement. *Ann Thorac Surg* 12:236, 1943.
129. Gordis, L., Lilienfeld, A. & Rodriguez, R.: Studies in the epidemiology and preventability of rheumatic fever. *J Chron Dis* 21:655, 1969.
130. Gordis, L., Lilienfeld, A. & Rodriguez, R.: An evaluation of the Maryland rheumatic fever registry. *Public Health Rep* 84:333, 1969.
131. Gordis, L. & Markowitz, M.: Prevention of rheumatic fever revisited. *Pediatr Clin North Am* 18:1243, 1971.
132. Gray, F.G., Quinn, R.W. & Quinn, J.P.: Rheumatic and non-rheumatic families. *Am J Med* 13:400, 1952.

133. Griffith, G.C., Moore, F.J., McGinn, S. & Cosby, R.S.: The familial incidence of rheumatic fever. *Am Heart J* 35:438, 1947.
134. Grist, N.R. & McLean, C.: Infections by organisms of psittacosis/lymphogranuloma venereum group in the west of Scotland. *Br Med J* 2:21, 1964.
135. Grosser, K.D.: Gegenwärtiger Stand der Elektrotherapie bei Vorhofflimmern. *Dtsch Med Wochenschr* 99:29, 1974.
136. Hall, P.: On the prognosis and natural history of acute rheumatic fever and rheumatic heart disease. *Acta Med Scand* (Suppl) 169, 1961.
137. Hanafiah, A.: Epidemiology of rheumatic fever and rheumatic heart disease in Indonesia. *Jpn Circ J* 39:189, 1975.
138. Handjani, A.M., Bolandgray, A. & Eghtedari, A.: Grand multiparity and rheumatic heart disease. *Obstet Gynecol* 32:210, 1968.
139. Harker, L. A. & Slichter, S.J.: Studies of platelet and fibrinogen kinetics in patients with prosthetic heart valves. *N Engl J Med* 283:1302, 1970.
140. Hasonova, V.A., Tarasevich, N.N., Bronzov, I.A. & Nanaeva, G.K.: Anticardiac antibodies reacting with the membranes of streptococcus in protracted rheumatic fever. *Kardiologia* 15:32, 1975.
141. Hassell, T.A., Renwich, S. & Stuart, K.L.: Rheumatic fever and rheumatic heart disease in Barbados: Detection and prophylaxis. *Br Med J* 3:387, 1972.
142. Hassell, T.A. & Stuart, K.L.: Rheumatic fever prophylaxis. *Br Med J* 2:39, 1940.
143. Hayes, C.J., Butler, V.P. Jr. & Gersony, W.M.: Serum digoxin studies in infants and children. *Pediatr* 52:561, 1973.
144. Haygarth, J.: Cited by Hedley, O.F., 1940.
145. Hedley, O.F.: Rheumatic heart disease in Philadelphia hospitals. *Public Health Rep* 55:1599, 1940.
146. Helfant, R.F.: Congenital compared with acquired valvular aortic stenosis. *Cardiovasc Clin* 5:65, 1973.
147. Hellgren, L.: The prevalence of rheumatoid arthritis in different geographical areas in Sweden. *Acta Rheum Scand* 16:293, 1970.
148. Henze, A. & Fortune, L.: Regurgitation and haemolysis in artificial heart valves. *J Thorac Cardiovasc Surg* 8:167, 1974.
149. Herr, R.H., Starr, A., Pierie, W.R., Wood, J.A. & Bigelow, C.: Aortic valve replacement. *Ann Thorac Surg* 6:199, 1968.
150. Hess, E.V., Fink, C.W., Taranta, A. & Ziff, M.: Heart muscle antibodies in rheumatic fever and arteriosclerosis. *J Clin Invest* 43:886, 1964.
151. Hirose, K. & Takao, A.: Decreasing incidence of JMS in Japan and post-operative history. *Jpn Circ J* 39:200, 1975.
152. Hoeschen, R.J. & Proveda, R.T.: Serum digoxin by radioimmunoassay. *Can Med Assoc J* 105:170, 1971.

153. Hollander, J.L. & McCarty, D.: Pathogenesis. In: Arthritis and allied conditions. Lea and Febriger, Philadelphia 1966.
154. Homma, M.: Studies of acute rheumatic fever in the adult. Jpn Circ J 33:1497, 1969.
155. Homma, M., Sakamoto, K. & Yamagata, H.: Prevention of rheumatic heart disease follow-up studies of adult rheumatic fever under oral prophylaxis with penicillin. Jpn Circ J 39:194, 1975.
156. Hong, C.Y.: The epidemiology of rheumatic fever and rheumatic heart disease in Korea. Jpn Circ J 39:182, 1975.
157. van der Horst, R.L., le Roux, B.T., Rogers, N.M. & Gotsman, M.S.: Mitral valve replacement in childhood. Am Heart J 85:624, 1973.
158. Hutchinson, E.C. & Stock, J.P.: Paroxysmal cerebral ischaemia in rheumatic heart-disease. Lancet 2:653, 1963.
159. Ilyas, M.R.C.: Secondary prevention of rheumatic heart disease in Pakistan. Jpn Circ J 39:194, 1975.
160. Jansen, H.H.: Morphologie der allergischen Erkrankungen des Menschen. Dtsch Med J 21:971, 1970.
161. Johansson, B.W.: Complete heart block. Acta Med Scand (Suppl) 180, 1966.
162. John, S., Gupta, R.P., Milledge, J.S., Munsli, S.C. & Cherian, G.: Results of mitral valve replacement in young patients with rheumatic heart disease. Circulation (Suppl) 45 and 46, 1972.
163. Johnson, E.E., Stollerman, G.H. & Grossman, B.J.: Rheumatic recurrences in patients not receiving continuous prophylaxis. JAMA 190:497, 1964.
5. Jones'criteria (modified). Committee on standards and criteria for programs of care. 24:291, 1955.
6. Jones'criteria. American Heart Association. Circulation 13:617, 1956.
164. Jonsell, S.: Method for determination of heart size by teleroentgenography (heart volume index). Acta Radiol 20:325, 1939.
165. Jonsson, B.: När skall vitier opereras? Forskning och Praktik (Sandoz) 10:17, 1978.
166. Joorabchi, B., Tahernia, A., A.C., Gharib, R. & Sadeghi, P.: Epidemiology of rheumatic heart disease in Iran. J Trop Med Hyg 74:203, 1974.
167. Kakvan, M. & Wright, T.M.: Criteria for surgery and choice of valve prostheses in patients with rheumatic heart disease. RI Med J 57:503, 1974.
168. Kaplan, M.H.: Autoimmunity to heart and its relation to heart disease. Prog Allergy 13:408, 1969.
169. Kaplan, M.H.: Immunologic relation of streptococcal and tissue antigens. J Immunol 90:595, 1963.
170. Kaplan, M.H., Meyeserian, M. & Kushner, I.: Immunologic studies of heart tissue. J Exp Med 113:17, 1961.

171. Kaplan, M.H. & Meyeserian, M.: An immunological cross-reacting between group-A streptococcal cells and human heart tissue. *Lancet* 1:706, 1962.
172. Kaster, R.L., Lillehei, C.W. & Starek, P.J.: The Lillehei-Kaster pivoting disc aortic prostheses and a comparative study of its pulsatile flow characteristics with four other prostheses. *Trans Am Soc Artif Intern Organs* 16:233, 1970.
173. Kawakita, S., Takeuchi, T., Uemura, Y., Onishi, T., Saito, K., Nagami, H. & Watanebe, T.: The role of upper respiratory infections of group A streptococci to rheumatic fever. *Jpn Circ J* 39:164, 1975.
174. Kelle, F., Fekecs, B., Gröh, V., Házas, J., Lassu, G. & Keleman, K.: Ätiopathogenese und klinische Aspekte der Myokarditis. *Z Aerztl Fortbild* 69:1023, 1975.
175. Kellogg, F., Liu, C.K., Fishman, W. & Larson, R.: Systemic and pulmonary emboli before and after mitral commissurotomy. *Circulation* 24:263, 1961.
176. Kiselev, R.A.: Contractile activity of the uterus in the pregnant with rheumatic affection of the heart during antirheumatic therapy. *Vopr Okhr Materin Det* 18:28, 1973.
177. Kitada, M., Uheda, K. & Yasutake, K.: Epidemiological features of rheumatic fever and rheumatic heart disease among school-children in Osaka. *Jpn Circ J* 39:187, 1975.
178. Klein, W. & Klein, G.: Zur Therapie und Prophylaxe der Herzentzündung nach Mitralfehlerkorrekturen am eröffneten Herzen. *Wien Med Wochenschr* 51:330, 1970.
179. Klein, W. & Klein, G.: Zur differentialdiagnostischen Verwertbarkeit erhöhter Antistreptolysintiter. *Wien Med Wochenschr* 51:160, 1970.
180. Korsgren, M., Leskinen, E., Peterhoff, V., Bradley, E. & Varnauskas, E.: Conversion of atrial arrhythmias with DC shock. *Acta Med Scand (Suppl)* 431, 1965.
181. Krause, R.M.: Prevention of streptococcal sequelae by penicillin prophylaxis: A reassessment. *J Infect Dis* 131:592, 1975.
182. Krivitsky, Ya.E. & Antonenko, B.N.: The state of the ovarian function in women suffering from rheumatism and rheumatic heart disease. *Akush Ginekol* 10:46, 1975.
183. Kudryavtseva, E.N. & Polunin, V.S.: Clinico-social investigations of rheumatic fever. *Vopr Revm* 4:48, 1974.
184. Kumagai, N.: Rheumatic fever and streptococcal infection anti-streptococcal antibodies in rheumatic fever and rheumatic heart disease. *Jpn Circ J* 39:167, 1975.
185. Kusakawa, S., Asai, T., Kiguchi, H., Nagai, Y. & Sonobe, T.: Treatment and long-term prognosis of rheumatic fever. *Jpn Circ J* 39:175, 1975.
186. Kuttner, A.G. & Mayer, F.E.: Carditis during second attacks of rheumatic fever. *N Engl J Med* 268:1259, 1963.

187. Kyrge, K.Kh., Birkenfeld, R.R. & Kyiv, E.A.: Relation between rheumatism incidence and meteorological factors. *Vopr Revm* 1:44, 1971.
188. Kästner, P., Günther, O. & Leutritz, S.: Zur Erfolgsbeurteilung der Tonsillektomie aus internistischer Indikation. *Z Gesamte Inn Med* 25:822, 1970.
189. Laboratory of physiological hygiene, University of Minnesota. Classification of the electrocardiogram for population studies. *Circulation* 19:314, 1959.
190. Lancefield, R.C.: Current knowledge of type-specific M antigens of group A streptococi. *J Immunol* 89:307, 1962.
191. Landahl, S., Lindblad, B., Roupe, S., Steen, B. & Svanborg, A.: Digitalis therapy in a 70-year-old population. *Acta Med Scand* 202:437, 1977.
192. Larsson, C., Dirksen, H., Sundström, G. & Eriksson, S.: Lung function studies in asymptomatic individuals with moderately (Pi SZ) and severely (Pi Z) reduced levels of alfa₁-antitrypsin. *Scand J Respir Dis* 57:267, 1976.
193. Laurell, C-B.: Electroimmuno Assay. *Scand J Lab Clin Invest (Suppl)* 124:21, 1972.
194. Lessof, M.: Sydenham's chorea. *Guy's Hospital Reports* 107:185, 1958.
195. Levison, D.A., Guthrie, W., Ward, C., Green, D.M. & Robertson, P.G.: Infective endocarditis as part of psittacosis. *Lancet* 2:844, 1971.
196. Lewis-Johnsson, J.: Chorea. *Acta Paediatr Scand (Suppl)* 73, 1949.
197. Linos, A., Worthington, J., O'Fallon, M. & Kurland, L.: The epidemiology of rheumatoid arthritis in Rochester. *Am J Epidemiol* 111:87, 1980.
198. Lower, R.R.: Current status of clinical cardiac transplantation. *Transplant Proc* 6:107, 1974.
199. Lue, H.C., Chen, C.M., Hsu, J.Y., Chen, C.L. & Wei, H.: Prevalence of rheumatic heart disease in the young in northern Taiwan 1970-1971. *Jpn Circ J* 39:188, 1975.
200. Lunds Universitets Datacentral. Statistical package for the social sciences.
201. Mahajan, G.M., Bidwai, P.S., Berry, J.N. & Walia, B.N.: Rheumatic fever and rheumatic heart disease in children in North India. *India J Pediatr* 39:332, 1972.
202. Malik, G.B.: Significance and incidence of Aschoff body in surgically removed auricular appendage. *Postgrad Med J* 18:101, 1972.
203. Manabe, H.: Valvotomy in young patients with rheumatic mitral stenosis. *Jpn Circ J* 39:199, 1975.
204. Marcus, D.M.: The ABO and Lewis Blood-group system. *N Engl J Med* 280:994, 1969.
205. Markowitz, M. & Denny, F.W.: Programs for the primary and secondary prevention of rheumatic fever. *Am Heart Assoc* 1971.

206. Markowitz, M. & Gordis, L.: The changing pattern of rheumatic fever. Rheumatic fever. In: Major problems in clinical pediatrics, pp. 1-13, 1972.
207. Markowitz, M. & Gordis, L.: The biology of group A beta hemolytic streptococci. Rheumatic fever. In: Major problems in clinical pediatrics, pp. 14-146, 1972.
208. Markowitz, M. & Kuttner, A.G.: Rheumatic fever. Diagnosis, management and prevention. In: Major problems in clinical pediatrics. pp. 11:1364. Philadelphia 1965.
209. Martelli, V., Ansbro, J.F. & Ross, D.N.: Isolated aortic valve replacement. *Isr J Med Sci* 11:173, 1975.
210. Massell, B.F.: Factors in the pathogenesis of rheumatic fever: A study of streptococcal infections and rheumatic fever. *J Maine Med Assoc* 53:88, 1962.
211. Massell, B.F., Amezcua, F. & Pelargonio, S.: Evolving picture of rheumatic fever. *JAMA* 188:297, 1964.
212. Massell, B.F., Honikman, L.H. & Amezcua, F.: Rheumatic fever following streptococcal vaccination. *JAMA* 207:1115, 1969.
213. Mayer, F.E., Doyle, E.F., Herrera, L. & Brownell, K.D.: Declining severity of first attack of rheumatic fever. *Am J Dis Child* 105:146, 1963.
214. McCarty, M.: Theories of pathogenesis of streptococcal complications. In: Streptococci and streptococcal diseases. Recognition, Understanding and Management (ed. L.W. Wannamaker and J.M. Matsen), pp. 517-526. Academic Press, New York 1972.
215. McDevitt, E.: Anticoagulant therapy. In: Cerebral vascular diseases. (ed. Millikan, Siekert and Whisnant), pp. 90-93. Grune and Stratton, New York 1965.
216. McKee, P.A., Castelli, W.P., McNamara, P.M. & Kannell, W.B.: The natural history of congestive heart failure: The Framingham study. *N Engl J Med* 285:1441, 1971.
217. McLaren, M.J., Hawkins, D.M., Koornhof, H.J., Bloom, K.R., Bramwell-Jones, D.M., Cohen, E., Gale, G.E., Kanarek, K., Lachman, A.S., Lakier, J.B., Pocock, W.A. & Barlow, J.B.: Epidemiology of rheumatic heart disease in black school-children of Soweto, Johannesburg. *Br J Med* 3:474, 1975.
218. Medical Research Council of Great Britain and American Heart Association: The evolution of rheumatic heart disease in children. *Circulation* 22:503, 1960.
219. Medical Research Council of Great Britain and American Heart Association: The natural history of rheumatic fever and rheumatic heart disease. *Circulation* 32:457, 1965.
220. Metcalfe, J.: Rheumatic heart disease in pregnancy. *Obstet Gynecol* 11:1010, 1968.

221. Mihalcu, F., Poetas, M., Croitorescu, M. & Stoia, I.: The value of some immunological indexes in the diagnosis of inflammatory rheumatism. *Microbiol Parazitol Epidemiol* 15:407, 1970.
222. Mikkelsen, W.M.: The epidemiology of rheumatic diseases. In: *Arthritis and Allied Conditions* (ed. J. Hollander and D.J. McCarty). pp. 211-220. 1972.
223. Misu, R.: Natural history of rheumatic valvular heart disease, correlation of clinical data with autopsy findings. *Bull Heart Inst Jpn* 14:164, 1972.
224. Morton, W.: Altitude and rheumatic fever in Colorado. *Am J Epidemiol* 83:250, 1965.
225. Morton, W., Huhn, L.A. & Litchy, J.A.: Rheumatic heart disease epidemiology. *JAMA* 199:879, 1967.
226. Morton, W. & Lichty, J.A.: Rheumatic heart disease. *Am J Epidemiol* 92:113, 1970.
227. Morton, W., Warner, A.L., Weil, J.V., Shmook, C.L., Snyder, J. & Lichty, J.A.: Rheumatic heart disease epidemiology. *Circulation* 41:773, 1970.
228. Munoz, S., Gallardo, J., Diaz-Gorria, J.R. & Medina, O.: Influence of surgery on the natural history of rheumatic mitral and aortic valve disease. *Am J Cardiol* 35:234, 1975.
229. Nair, D.V.: Natural history rheumatic heart disease seen in Kerala state. *Jpn Circ J* 39:179, 1975.
230. Nair, D.V.: Prevention of rheumatic heart disease in school children. *Jpn Circ J* 39:193, 1975.
231. Naumann, P., Schmidt, W.A. & Rosin, H.: Die Erreger entzündlicher Herzkrankheiten. *Z Kardiol* 62:1066, 1973.
232. Nesterov, A.I.: Some new data on the progress of theoretical and practical rheumatology. *Sov Med* 33:3, 1970.
233. Noonan, J.A.: Natural history of rheumatic heart disease in adolescents. *Postgrad Med J* 56:107, 1974.
234. Novikov, Yu.I. & Stulova, M.A.: Viral affections of the heart. *Klin Med* 52:23, 1974.
235. Nyman, M.: Serum Haptoglobin. *Scand J Clin Lab Invest (Suppl)*, 1959.
236. O'Brien, M.F., Neilson, G.H., Galea, E.G., Molphy, R., Power, W., Lomas, C. & Stephens, J.: Heterograft valves. *Circulation (Suppl)* 41:16, 1970.
237. Oda, T.: Preventability of streptococcal infection by means of prophylactic medication of oral penicillin against rheumatic fever recurrence. *Jpn Circ J* 39:196, 1975.
238. Okuni, M. & Fujikawa, S.: Antistreptococcal polysaccharide level in the diagnosis for rheumatic fever. *Jpn Circ J* 39:171, 1975.
239. Olesen, K.H.: *Mitral stenosis*. Ejnar Munksgaards Forlag, Copenhagen, 1955.

240. Oliver, G.C., Parker, B.M. & Parker, C.W.: Radioimmunoassay for digoxin. *Am J Med* 51:186, 1971.
241. Olney, M.B.: Rheumatic fever in children. *Postgrad Med J* 41:592, 1967.
242. Oshima, M.: Rheumatic carditis in children. *Jpn Circ J* 30:1326, 1966.
243. Owren, P.A.: The results of anticoagulant therapy. *Arch Intern Med* 111:240, 1963.
244. Pacifico, A.D., Karp, R.B. & Kirklin, J.W.: Homografts for replacement of the aortic valve. *Circulation* 45:36, 1972.
245. Padmavati, S.: Epidemiology of cardiovascular disease in India. *Circulation* 25:703, 1962.
246. Pearce, J.: Susceptibility of heart of rabbit to specific infection in viral diseases. *Arch Path* 34:319, 1942.
247. Perry, C.B.: The natural history of acute rheumatism the lumleian lecture of the royal college of physicians, 1969. *Ann Rheum Dis* 28:471, 1969.
248. Persson, S.: Aortic valvular disease. *Studentlitteratur Lund*, 1974.
249. Petz, L.D. & Goodman, J.R.: Ringed sideroblasts and intramito-chondrial iron in cases of mechanical hemolytic anemia. *Ann Intern Med* 64:635, 1966.
250. Pilapil, V.R. & Watson, D.G.: Rheumatic fever in Mississippi. *JAMA* 215:1626, 1971.
251. Pitcairn, D.: Cited by Wilson, M.G., 1940.
252. Prasad, S.: Observations on seasonal, socio-economic, & heredo-familial factors of rheumatic heart disease in children. *Indian J Pediatr* 4:290, 1967.
253. Quinn, R.W. & Federspiel, C.F.: The incidence of rheumatic fever in Metropolitan Nashville, 1963-1969. *Am J Epidemiol* 99:273, 1974.
254. Quinn, R.W. & Liao, S.J.: A comparative study of antihyaluronidase, anti-streptolysin "O", antistreptokinase, and streptococcal agglutination titers in patients with rheumatic fever, acute hemolytic streptococcal infections, rheumatoid arthritis and non-rheumatoid forms of arthritis. *J Clin Invest* 29:1156, 1950.
255. Quinn, R.W. & Quinn, J.P.: Mortality due to rheumatic heart disease in the socio-economic districts of New Haven, Connecticut. *Yale J Biol Med* 24:15, 1951.
256. Quinn, R.W., Sprague, A. & Quinn, J.P.: Mortality rates for rheumatic fever and rheumatic heart disease, 1940-1965. *Public Health Rep* 85:1091, 1970.
257. Reichel, N., Shelburne, J.C. & Perloff, J.K.: Clinical aspects of rheumatic valvular disease. *Prog Cardiovasc Dis* 15:491, 1973.
258. Reuschel, I., Reinelt, D. & Gruber, G.: Diagnostik und Verlaufsbeurteilung des rheumatischen Fiebers. *Z Gesamte Inn Med* 29:757, 1974.
259. Roberts, W.C.: Anatomically isolated aortic valvular disease. *Am J Med* 49:151, 1970.

260. Rodgers, B.M. & Sabiston, D.: Hemolytic anemia following prosthetic valve replacement. *Circulation* 39:1955, 1969.
261. Roger, H.: Cited by Jacobsson, E., 1946. *Acta Paediatr Scand* (Suppl) 63, 1946.
262. Rolicka, M. & Massell, B.F.: Antipeptidoglycan in rheumatic fever: Agreement with carditis. *Proc Soc Exp Biol Med* 144:892, 1973.
7. Ropes, M.W., Bennett, G.A., Cobb, S., Jacox, R. & Jessar, R.A.: Proposed diagnostic criteria for rheumatoid arthritis. *Bull Rheum Dis* 7:121, 1956.
8. Ropes, M.W., Bennett, G.A., Cobb, S., Jacox, R. & Jessar, R.A.: Revision of diagnostic criteria for rheumatoid arthritis. *Bull Rheum Dis* 9:175, 1958.
263. Rotman, M., Morris, J.H., Behar, V.S., Peter, R.H. & Kong, Y.: Aortic valvular disease. *Am J Med* 51:241, 1971.
264. Roy, S.B.: Challenge of juvenile mitral stenosis in India. *Jpn Circ J* 39:188, 1975.
265. Sainani, G.S., Krompotic, E. & Slodki, S.J.: Heart disease due to coxsackie virus B infection. *Medicine* 47:133, 1968.
266. Saksena, P.N., Kapoor, V.K. & Kumar, N.: Rheumatic fever. *Indian J Pediatr* 36:1, 1969.
267. Sanner, E.: *Klaffel. Läkartidningen* 74:2558, 1977.
268. Sanyal, S.K., Thapar, M.K., Ahmed, S.H., Hooja, V. & Tewari, P.: The initial attack of acute rheumatic fever during childhood in north India. *Circulation* 49:7, 1974.
269. Sashenkova, V.P. & Chebotareva, V.N.: Peculiarities of rheumatism in children during the last decade. *Vopr Okhr Materin Det* 16:21, 1971.
270. The Scandinavian Committee on ECG Classification: The "Minnesota code" for ECG classification adaptation to CR leads and modification of the code for ECGs recorded during and after exercise. *Stockholm* 1967.
271. Schick, B.: "Die Nachkrankheiten des Scharlach". *Jb Kinderheilk* (Suppl) 65, 1907.
272. Schmidt, G.: Elektroenzephalographie und Prognose der Rheumatischen Encephalopathie im Kindesalter. *Beitr Rheumatol* 15:101, 1970.
273. Selzer, A. & Cohn, K.E.: Natural history of mitral stenosis. *Circulation* 45:878, 1972.
274. Setty, M.R., Shadaksharappa, K.S., Madappa, N. & Setty, G.: Chronic rheumatic heart disease in Bangalore. *Indian Heart J* 24:253, 1972.
275. Shaper, A.G.: Cardiovascular disease in the tropics. *Br Med J* 3:683, 1972.
276. Shiokawa, Y.: Streptococcus surveys in Indonesia and India. *Jpn Circ J* 39:172, 1975.
277. Shiokawa, Y.: Past, present and future of rheumatic fever and rheumatic heart disease in Japan. *Jpn Circ J* 37:171, 1973.

278. Shiokawa, Y.: Streptococcus surveys in Ryukyu Islands, Japan. *Jpn Circ J* 39:168, 1975.
279. Shiokawa, Y.: Epidemiology of rheumatic fever and rheumatic heart disease in Japan. *Jpn Circ J* 39:185, 1975.
280. Shiokawa, Y.: Study on the chemoprophylaxis of rheumatic heart disease. *Jpn Circ J* 39:178, 1975.
281. Shiokawa, Y. & Murakami, M.: Epidemiology of rheumatic fever and rheumatic heart disease in Japan. *Jpn Circ J* 33:1490, 1969.
282. Shulman, S. & Ayoub, E.M.: The control of rheumatic fever. *Clin Pediatr* 14:319, 1975.
283. Shulman, S., Victorica, B.E. & Ayoub, E.M.: Abdominal pain in acute rheumatic fever. *Clin Pediatr* 10:610, 1971.
284. Siekert, R.G.: Anticoagulant therapy. In: *Cerebral vascular disease* (ed. Millikan, Siekert & Whisnant), pp. 94-105. Grune and Stratton, New York 1965.
285. Sievers, J. & Hall, P.: Incidence of acute rheumatic fever. *Br Heart J* 33:833, 1971.
286. Sitaj, S., Urbánek, T. & Bosmansky, K.: Some aspects of epidemiology and surveillance of rheumatic fever. *Acta Rheum Scand* 16:30, 1970.
287. Smith, W.G.: Adult heart disease due to the coxsackie virus group B. *Br Heart J* 28:204, 1966.
288. Somer, T.: Rheumatic fever. *Duodecim* 88:977, 1972.
289. Sowinska, J.: Immunologic phenomena in the heart in rheumatic fever. *Mater Med Pol* 6:29, 1974.
290. Spagnuolo, M. & Feinstein, A.R.: Congestive heart failure and rheumatic activity. *Pediatr* 33:653, 1964.
291. Spagnuolo, M., Kloth, H., Taranta, A., Doyle, E. & Pasternack, B.: Natural history of rheumatic aortic regurgitation. *Circulation* 44:368, 1971.
292. Spagnuolo, M., Pasternack, B. & Taranta, A.: Risk of rheumatic fever recurrences after streptococcal infections. *N Engl J Med* 285:642, 1971.
293. Spodick, D.: Rheumatic heart disease in south Africa. *Br Med J* 4:579, 1975.
294. Starr, A., Bonchek, L.E., Anderson, R.P., Wood, J. A. & Chapman, R.D.: Late complications of aortic valve replacement. *Ann Thorac Surg* 19:289, 1975.
295. Starr, A. & Edwards, L.: Mitral replacement. *Ann Surg* 154:726, 1961.
296. Steele, P., Weily, J., Davies, H., Pappas, G. & Genton, E.: Platelet survival time following aortic valve replacement. *Circulation* 51:358, 1975.
297. Stehbens, J.A. & Macqueen, J.C.: The psychological adjustment of rheumatic fever patients with and without chorea. *Clin Pediatr* 11:638, 1972.

298. Stevenson, A.C. & Cheeseman, E.A.: Heredity and rheumatic fever. *Ann Hum Genet* 17:177, 1953.
299. Stollerman, G.: A scarlatinal "Nachkrankheit" of Schick: Rheumatic fever, 50 years later. *Int Arch Allergy* 12:287, 1958.
300. Stollerman, G.: Factors determining the attack of rheumatic fever. *JAMA* 177:823, 1961.
301. Stollerman, G.: The epidemiology of primary and secondary rheumatic fever. In: *The streptococcus rheumatic fever and glomerulonephritis.* (ed. J.W. Uhr), pp. 311-329. Williams and Wilkins, Baltimore 1964.
302. Stollerman, G.: Nephritogenic and rheumatogenic group A streptococci. *J Infect Dis* 120:258, 1969.
303. Stollerman, G., Markowitz, M., Taranta, A., Wannamaker, L. & Whittemore, R.: Jones' criteria (revised) for guidance in the diagnosis of rheumatic fever. *Circulation* 32:664, 1965.
304. Stollerman, G. & Pearce, I.: The changing epidemiology of rheumatic fever and acute glomerulonephritis. *Adv Intern Med* 14:210, 1968.
305. Strasser, T.: Controllo della febbre rheumatica. *Clin Ter* 59:15, 1971.
306. Strasser, T.: Rheumatic fever and the health of population. *Jpn Circ J* 39:174, 1975.
307. Strasser, T.: Rheumatic fever and rheumatic heart disease in the 1970s. *WHO Chron* 32:18, 1978.
308. Strasser, T. & Rotta, J.: The control of rheumatic fever and rheumatic heart disease: an outline of WHO activities. *WHO Chron* 27:49, 1973.
309. Strauss, W. & Goldring, D.: Valve replacement in acute rheumatic heart disease. *J Pediatr* 84:786, 1974.
310. Strauss, W., Goldring, D., Kissane, J., Hernandez, A., Hartmann, A.F., McKnight, C.R. & Weldon, C.S.: Valve replacement in acute rheumatic heart disease. *J Thorac Cardiovasc Surg* 67:659, 1970.
311. Sun, S.C., Sohal, R.S., Burch, G.E., Chu, K.C. & Colcolough, H.L.: Coxsackie virus B₄ pancarditis in cynomolgus monkeys resembling rheumatic heart lesions. *Br J Exp Pathol* 48:655, 1967.
312. Sundström, G.: Influence of ventilation, exercise, and body position on techniques for determining steady state diffusing capacity. *Scand J Respir Dis (Suppl)* 92:18, 1975.
313. Swedner, H.: Exempel på olika typer av indelningar i samhällsklasser och socialgrupper. In: *Arbetsmaterial till metodkurs för ett betyg i sociologi.* (ed. A Hallström, G. Lindberg, A. Mullaert och H. Swedner), pp. 19:1-19:40. Studentlitteratur, Lund 1969.
314. Sydenham, T.: Cited by Wilson, M.G., 1940.
315. Szekely, P.: Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *Br Med J* 1:1209, 1964.

316. Tahernia, A.C., Moatamed, F. & Sharif, H.: Some clinical observations on rheumatic fever in childhood. *Clin Pediatr* 10:530, 1971.
317. Takashina, Y., Uheda, K., Yanagida, G., Kitada, M. & Hosokawa, K.: Rheumatic heart disease in Osaka children. *Jpn Circ J* 33:1521, 1969.
318. Takeda, J., Warren, R. & Holzman, D.: Prognosis of aortic stenosis. *Arch Surg* 87:931, 1963.
319. Tamer, D.M.: Acute rheumatic fever in a south Florida County Hospital, 1967-1971. *Circulation* 50:765, 1974.
320. Taranta, A.: Factors influencing recurrent rheumatic fever. *Annu Rev Med* 18:159, 1967.
321. Taranta, A.: Rheumatic fever: Pathology, etiology, epidemiology and pathogenesis. In: *Arthritis and allied conditions*. (ed. J.L. Hollander and D.J. McCarty Jr), pp. 736-763. Philadelphia 1972.
322. Taranta, A., Fiedler, J., Frank, C.W., Gilson, B.S., Gordis, L., Hufnagel, C., Markowitz, M. & Wannamaker, L.W.: Prevention of rheumatic fever and rheumatic heart disease. *Circulation* 41:1, 1970.
323. Taranta, A. & Gordis, L.: The prevention of rheumatic fever: Opportunities, frustrations, and challenges. *Cardiovasc Clin* 4:1, 1972.
324. Taranta, A., Kleinberg, E., Feinstein, A., Wood, H.F., Tursky, E. & Simpson, R.: Rheumatic fever in children and adolescents. *Ann Intern Med* (Suppl) 60:58, 1964.
325. Taranta, A., Spagnuolo, M. & Feinstein, A.R.: "Chronic" rheumatic fever. *Ann Intern Med* 56:367, 1962.
326. Taranta, A. & Stollerman, G.H.: The relationship of Sydenham's chorea to infection with group A streptococci. *Am J Med* 20:170, 1956.
327. Tedesco, F., Liso, V. & Tursi, A.: R.A. test, Waaler-Rose, Heller-F_{II}. *Reumatismo* 20:5, 1968.
328. Thorell, J. & Larsen, S.: Pharmacologic digoxin. In: *Radioimmunoassay and related techniques*. pp. 242-248. The C.V. Mosby Company, Saint Louis 1978.
329. Thorson, A. & Waldenström, J.: Studies on carcinoid disease. *Acta Med Scand* (Suppl) 161, 1958.
330. Tichy, H.: Die Verteilung serologischer Reaktionswerte in den Hauptgruppen der rheumatischen Krankheiten auf Grund von 11379 Fällen der Jahre 1953-1962. *Z Gesamte Inn Med* 24:211, 1969.
331. Timmis, H.H., Hardy, J.D., Watson, D.G. & Blake, T.M.: Mitral valve replacement in a child during active rheumatic carditis. *Ann Surg* 164:1034, 1966.
332. Todd, E.W.: Antihaemolysis titres in haemolytic streptococcal infections and their significance in rheumatic fever. *Br J Exp Pathol* 13:248, 1932.
333. Toh, C.C.: Juvenile mitral stenosis. *Jpn Circ J* 39:198, 1975.

334. Turner, R.W.: Controversial aspects of rheumatic heart disease. *Br Med J* 2:383, 1968.
335. Tybjaerg-Hansen, A.: Present status of the prevention of rheumatic heart disease in Denmark. Paper read at the Vth World Congress of Cardiology, New Delhi 1966.
336. Uchida, I.A.: Possible genetic factors in the etiology of rheumatic fever. *Am J Hum Genet* 5:61, 1952.
337. Vaccaro, R.: Sul significato dei fattori serici cuore-reagenti osservabili nella fase acuta della malattia reumatica. *Minerva Med* 63:2314, 1972.
338. Vaccaro, R. & Ramenghi, M.: La malattia reumatica nell'infanzia annotazioni d'aggiornamento clinico e patogenetico. *Recenti Prog Med* 50:538, 1971.
339. Vazquez, J.J. & Dixon, F.J.: Immunohistochemical study of lesions in rheumatic fever, systemic lupus erythematosus, and rheumatoid arthritis. *Lab Invest* 6:205, 1957.
340. Vorlaender, K.O. & Lorbacher, P.: Zur Pathogenese und Klinik immunpathologischer Erkrankungen. *Verh Dtsch Ges Inn Med* 74:724, 1968.
341. Waaler, E.: Rheumatic fever and rheumatic heart disease. *Acta Med Scand* 160:281, 1958.
342. Waaler, E.: Rheumatic fever and rheumatic heart disease. *Acta Med Scand* 160:293, 1958.
343. Waldmann, G.: Zur Pathogenese der Myocarditis rheumatica. *Beitr Rheumatol* 17:11, 1971.
344. Wallace, W.A., Harken, D.E. & Ellis, L.B.: Pregnancy following closed mitral valvuloplasty. *JAMA* 217:297, 1971.
345. Walsh, J.R., Starr, A. & Ritzmann, L.W.: Intravascular hemolysis in patients with prosthetic valves and valvular heart disease. *Circulation (Suppl)* 39:135, 1969.
346. Wannamaker, L.W.: Differences between streptococcal infections of the throat and of the skin. *N Engl J Med* 282:78, 1970.
347. Wannamaker, L.W.: The chain that links the heart to the throat. *Circulation* 48:9, 1973.
348. Wannamaker, L.W. & Ayoub, E.M.: Antibody titers in acute rheumatic fever. *Circulation* 21:598, 1960.
349. Wannamaker, L.W. & Kaplan, E.L.: The modern face of rheumatic fever. *Cardiovasc Clin* 5:1, 1973.
350. Ward, C.: "Rheumatic" heart disease, psittacosis and the importance of epidemiology. *Am Heart J* 95:266, 1978.
351. Ward, C. & Deasy, P.F.: Rheumatic fever. *Isr J Med Sci* 3:415, 1970.
352. Watanabe, N.: Antihyaluronidase antibody in the patients with rheumatic fever. *Jpn Circ J* 39:157, 1975.

353. Watson, T.: Cited by Wilson, M.G., 1940.
354. Wedum, A.G. & Wedum, B.G.: Rheumatic fever in Cincinnati in relation to rentals, crowding, density of population, and negroes. *Am J Public Health* 34:1065, 1944.
355. Weily, H.S., Steele, P., Davies, H., Pappas, G. & Genton, E.: Platelet survival in patients with substitute heart valves. *N Engl J Med* 290:534, 1974.
356. Wells, W.C.: Cited by Wilson, M.G., 1940.
357. Wendler, H.: Über die Chorea minor und ihre Beziehungen zum rheumatischen Fieber. *Arch Kinderheilkunde* 181:218, 1970.
358. Werner, B.: Malmö och dess tillgreppsbrottlighet. En socialekologisk undersökning. Lunds Universitet, Lund 1963.
359. Wessler, S.: Anticoagulant therapy-1974. *JAMA* 228:757, 1974.
360. Wolkoszewski, E.: Rheumatic fever in children in the light of modern observations. *Pol Med J* 6:143, 1967.
23. 24. 47. 251. 314. 353. 356. Wilson, M.G.: Rheumatic fever; Studies of the epidemiology, manifestations, diagnosis and treatment of the disease during the first three decades. Commonwealth Fund, London, 1940.
361. Wilson, M.G. & Lim, W.N.: The natural history of rheumatic heart disease in the third, fourth, and fifth decades of life. *Circulation* 16:700, 1957.
362. Wilson, M.G. & Lim, W.N.: Short-Term hormone therapy: Its effect in active rheumatic carditis of varying duration. *N Engl J Med* 260:802, 1959.
363. Wilson, M.G., Lim, W.N. & Birch, A.M.: Decline of rheumatic fever. *J Clin Dis* 7:183, 1958.
364. Winblad, S.: Studies on agglutination of sensitized sheep cells in rheumatic diseases. I. Agglutination titer after primary absorption of serum by sheep cells. *Acta Med Scand* 142:450, 1952.
365. Winblad, S.: Studies on different laboratory test for the rheumatoid arthritis serum factor. 1. Evaluation of different agglutination methods for whole serum, cold-precipitate and euglobulin serum fractions. *Acta Pathol Microbiol Scand* 49:499, 1960.
366. Winblad, S.: Studies in the laboratory estimation of the rheumatoid arthritis serum factor. 2. Gamma globulin precipitation test in relation to haemagglutination test with sensitized sheep cells and acrylplast fixation test. *Acta Pathol Microbiol Scand* 49:515, 1960.
367. Winblad, S.: Studies in laboratory estimation of rheumatoid arthritis serum factor. 3. Slide agglutination methods with and without sensitizing gamma globulin. *Acta Pathol Microbiol Scand* 49:523, 1960.
368. Winblad, S.: Studies on non-specific antistreptolysin O titre. 1. The influence of serum beta-lipoproteins on the non-specific antistreptolysin O titre. *Acta Pathol Microbiol Scand* 66:93, 1966.

369. Winblad, S., Killander, J. & Philipson, L.: Studies on non-specific anti-streptolysin O titre. *Acta Pathol Microbiol Scand* 65:587, 1965.
370. Witczynska, M.: Incidence of rheumatic fever in children in the city of Bialystok. *Reumatologia* 11:159, 1973.
371. Wood, H. & McCarty, M.: Laboratory aids in the diagnosis of rheumatic fever and in evaluation of disease activity. *Am J Med* 17:768, 1957.
372. Wood, H., Simpson, R., Feinstein, A., Taranta, A., Tursky, E. & Stollerman, G.: Rheumatic fever in children and adolescents. *Ann Intern Med* (Suppl) 60:6, 1964.
373. Wood, P.: An appreciation of mitral stenosis. *Br J Med* 1:1051, 1954.
374. Wood, P.: Aortic stenosis. *Am J Cardiol* 1:553, 1958.
375. Wu, R.: Prevalence and pattern of rheumatic heart disease among chinese in Hong Kong. *Jpn Circ J* 39:184, 1975.
376. Wulff, H.B., Biörck, G., Bergh, N.P., Krook, H., Axén, O. & Lundskog, O.: Studies in mitral stenosis. *Acta Med Scand* 144:275, 1953.
377. Yacoub, M., Towers, M. & Somerville, W.: Results of mitral valve replacement using unstented fresh semilunar valve homografts. *Circulation* (Suppl) 45:44, 1972.
378. Yodfat, Y.: The prevalence of cardiovascular disease in different ethnic and socio-economic groups in Beit Shemesh, Israel. *Isr J Med Sci* 8:1685, 1972.
379. Zabriskie, J.B.: The relationship of streptococcal cross-reactive antigens to rheumatic fever. *Transplant Proc* 1:968, 1969.
380. Zabriskie, J.B. & Freimer, E.H.: An immunological relationship between antigens of group A streptococcus and mammalian muscle. *J Exp Med* 124:661, 1966.
381. Zitnan, D. & Bosmansky, K.: Antimyocardial factor in rheumatic fever. *Acta Rheumatol Scand* 12:267, 1966.

